INTRAVASCULAR VOLUME STATUS IN 1ST EPISODE OF NEPHROTIC SYNDROME

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CHENNAI

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INSTITUTE OF CHILD HEALTH AND

HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE,CHENNAI

CERTIFICATE

This is to certify that dissertation entitled "INTRAVASCULAR VOLUME STATUS IN 1ST EPISODE NEPHROTIC SYNDROME" submitted by Dr.V.P.KRISHNAN to the Faculty of Paediatrics, The Tamilnadu Dr . M.G.R. Medical University , Chennai in partial fulfilment of the requirement for the award of M.D. Degree (Paediatrics) is a bonafide research work carried out by her under direct supervision and guidance.

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I Dr.V.P.KRISHNAN solemnly declare that the dissertation titled "***INTRAVASCULAR STATUS IN 1ST EPISODE OF NEPHROTIC SYNDROME***" has been prepared by me. This is submitted to the Tamilnadu Dr . M.G.R. Medical University , Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in Paediatrics.

DATE : **DR.V.P.KRISHNAN**

PLACE :

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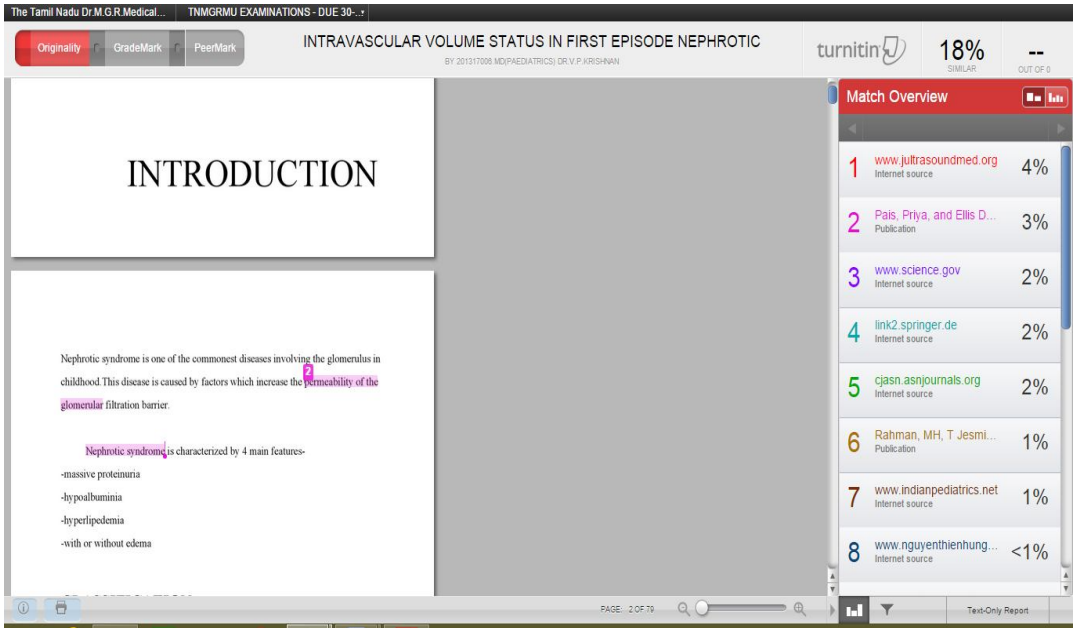
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INTRODUCTION
Nephrotic syndrome is one of the commonest diseases involving the glomerulus in childhood.This disease is caused by factors which increase the permeability of the glomerular filtration barrier.
Nephrotic syndrome is characterized by 4 main features-
-massive proteinuria
-hypoalbuminia
-hyperlipedemia
-with or without edema
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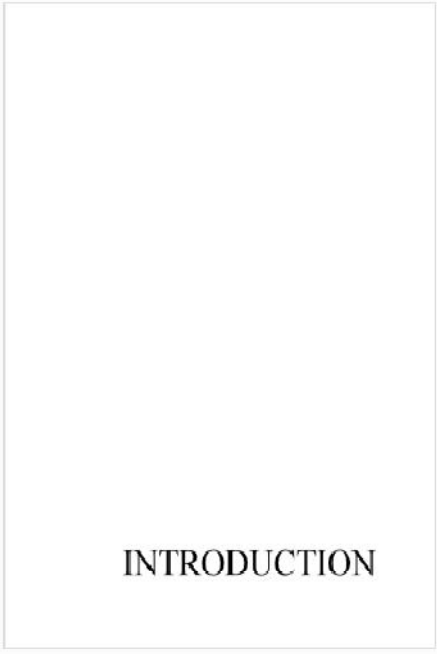


CONTENTS

INTRAVASCULAR VOLUME STATUS IN 1ST EPISODE OF NEPHROTIC SYNDROME-A SINGLE CENTER STUDY

ABSTRACT

Aim and Objectives: To assess the intravascular volume status in children presenting with first episode of Nephrotic Syndrome in our centre, ICH&HC, Madras Medical College Chennai.

Methodology-A prospective observational study was done on all children presenting with 1st episode of nephrotic syndrome based on inclusion and exclusion criteria in the general pediatric wards in ICH. 42 children who satisfied the inclusion and exclusion criteria between January-September 2015 were enrolled into the study. Detailed history and clinical examination were done for these patients. Tests for FeNa, Fractional urinary excretion of potassium, Echo to look for IVC collapsibility index was done for all of these patients on admission. Results were entered in an excel sheet and data was analyzed using open epi version 2.3.1 for statistics.

Results-This study included 42 participant 16(38.1%) were females and 26(61.9%) were males. 20(47.6%) patients were found to have a FeNa of < 1,whereas 22(52.4%) patients were found to have a value of FeNa >1. 16(38.1%) patients were found to have a fractional urinary excretion of potassium of > 60 %,whereas 26 (61.9%) patients in this study had a fractional urinary excretion of potassium of <60 %.A total of 16(38.1%) patients were found to a have an IVCCI < 50 %. 26(61.9 %) patients were found to have an IVCCI > 50 %. From the above values, hypovolemia was defined as having FENa<1 and Uk/Uk+Una>60% and IVC collapsibility > 50 %. In this study 16 (38.1%) patients had hypovolemia satisfying

the above criteria. 22(52.4%) patients had FeNa >1 and fractional urinary potassium excretion <60 % and IVCCI < 50 %. Hence these patients were classified as hypervolemic. 4(9.5%) patients had a FeNa <1 but fractional urinary potassium excretion <60 % and IVCCI < 50 %. Since these patients did not satisfy the criteria for hypovolemia fully, there were classified as having hypervolemic or normovolemic intravascular volume status. Hence a total of 16(38.1%) patients were classified as having hypovolemia whereas the rest of the 26(61.9 %) were classified as having hypervolemia or normovolemia(not having hypovolemia).

Conclusion- Intravascular volume status was found to be decreased/hypovolemic in 38% of the patients in this study whereas 62 % of the patients had hypervolemic or normovolemic intravascular status. Since a significant number of patients were found to be hypovolemic, intravascular volume status must be assessed in patients with 1st episode of nephrotic syndrome before the institution of diuretic therapy for treating edema.

Key words- 1st episode nephrotic syndrome, intravascular volume status, FeNa, Fractional urinary excretion of potassium, IVC collapsibility index.

INTRODUCTION

Nephrotic syndrome is one of the commonest diseases involving the glomerulus in Childhood . This disease is caused by factors which increase the permeability of the glomerular filtration barrier[1].

Nephrotic syndrome is characterized by 4 main features[1]-

-massive proteinuria

-hypoalbuminia

-hyperlipedemia

-with or without edema

CLASSIFICATION

ON THE BASIS OF AGE OF PRESENTATION[1]

Classification based upon the age of presentation is needed because of the variations in the underlying histology and management in the different groups

-<3 months of age-congenital nephrotic syndrome

-3m to1 yr-infantile nephrotic syndrome

->1 yr-childhood nephrotic syndrome

ON THE BASIS OF RESPONSIVENESS TO TREATMENT

-Steroid sensitive nephrotic syndrome-

Responsive to normal regimen of steroid with decrease in proteinuria and symptoms

-Steroid dependent nephrotic syndrome-

Two consecutive relapse during alternate day steroid regimen (or) Within 14 days of stopping steroids.

-Steroid resistant nephrotic syndrome-

Inability to induce remission in 8 weeks of full dose steroids.

ON THE BASIS OF HISTOLOGY

-Minimal change nephrotic syndrome-

Most common type of nephrotic syndrome in children. Accounts for about 90% of all the cases of all the nephrotic syndrome in childhood.

Light microscopy-normal

Immunoflurosence-negative

Electron microscopy-fusion of foot process

Response to steroids-90%

-Focal segmental glomerulosclerosis

Less common subtype.

May present with haematuria, hypertension, acute renal failure in addition to features of nephrotic syndrome.

Light microscopy-focal sclerotic lesions

Immunoflurosence-IgM, C3 in lesions

Electron microscopy-fusion of foot processes

Response to steroids-15-20%

-Membranous nephropathy

Less common subtype.

May present with haematuria,hypertension,acute renal failure in addition to features of nephrotic syndrome.

Associated with renal vein thrombosis,malignancy,SLE, Hepatitis B.

Light microscopy-Thickened GBM,spikes

Immunoflurosence-fine granular IgG ,C3

Electron microscopy-subepithelial deposits

Response to steroids-may be slow progression

-Membranoproliferative glomerulonephritis type 1

Less common subtype.

May present with haematuria,hypertension,acute renal failure in addition to features of nephrotic syndrome.

Light microscopy-Thikened GBM,proliferation

Immunoflurosence-Granular IgG,C3

Electron microscopy-mesangial and subendothelial deposits

Response to steroids-not yet established

-Membranoproliferative glomerulonephritis type 2

Less common subtype.

May present with haematuria,hypertension,acute renal failure in addition to features of nephrotic syndrome.

Associated with partial lipodystrophy.

Light microscopy-lobulation

Immunoflurosence-c3only

Electron microscopy-dense deposits

Response to steroids-not yet established

DEFINITION

NEPHROTIC SYNDROME[2]

+Proteinuria of more than

40 mg/m2/hr or

50 mg/kg/day or

Urine spot PCR >2 or urine dipstick> 2+ for 3 consecutive days.

+hypoalbuminia

As defined as serum albmin<2.5 gm/dl

+Hypercholestremia-

As defined by serum cholesterol>200

With or without edema.

REMISSION

Urine protein less than 0.4 mg/m2/hr or Spot PCR <0.2 or urinary dipstick trace or nil for 3 consecutive days.

RELAPSE

Urine protein more than 40 mg/m2/hr or Spot PCR >2.0 or urinary dipstick 3+ or more for 3 consecutive days

FREQUENT RELAPSE

2 or more relapses within 6 months of initial remission (or)

3 relapses in any 12 month period.

STEROID DEPENDENCE[2]

2consecutive relapses during alternate day steroid regimen or within 14days of stopping steroids.

STEROID RESISTANCE[2]

Inability to induce reimission to steroids within 8 weeks of full dose of steroids.

EPIDEMIOLOGY

Most common age group of presentation of nephrotic syndrome is 3- 6 yrs[1,7].Around 2/3rds present before 6 yrs of age.The ratio among boys to girls is 2:1.But by late adoloscence both sexes are equally affected.

About 90% of the patients are in the most common form known as Idiopathic Nephrotic syndrome.Rest of the 10 % may be divided into multiple forms.

Incidence is about 2-3 cases per 100000 children in developed countries with higher incidence in developing countries.

ETIOLOGY

[2]IDIOPATHIC NEPHROTIC SYNDROME

Minimal change disease

Focal segmental glomerulosclerosis

Membranous nephropathy

Glomerulonephritis associated with nephrotic syndrome–

membranoproliferative glomerulonephritis, crescentic

glomerulonephritis, immunoglobulin A nephropathy.

GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME

Nephrotic Syndrome (Typical)

Finnish-type congenital nephrotic syndrome (absence of nephrin)

Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)

Diffuse mesangial sclerosis (mutations in laminin β2 chain)

Denys-Drash syndrome (mutations in WT1 transcription factor)

Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation)

Mitochondrial disorders

Proteinuria With or Without Nephrotic Syndrome

Nail-patella syndrome (mutation in LMX1B transcription factor)

Alport syndrome (mutation in collagen biosynthesis genes)

Multisystem Syndromes With or Without Nephrotic Syndrome

Galloway-Mowat syndrome

Charcot-Marie-Tooth disease

Jeune syndrome

Cockayne syndrome

Laurence-Moon-Biedl-Bardet syndrome

Metabolic Disorders With or Without Nephrotic Syndrome

Alagille syndrome

α1-Antitrypsin deficiency

Fabry disease

Glutaric acidemia

Glycogen storage disease

Hurler syndrome

Partial lipodystrophy

Mitochondrial cytopathies

Sickle cell disease

SECONDARY CAUSES OF NEPHROTIC SYNDROME

+**Infections like**

Endocarditis

Hepatitis B, C

HIV-1

Infectious mononucleosis

Malaria

Syphilis (congenital and secondary)

Toxoplasmosis

Schistosomiasis

Filariasis

+**Drugs**

Captopril

Penicillamine

Gold

Nonsteroidal antiinflammatory drugs

Pamidronate

Interferon

Mercury

Heroin

Lithium

+Others

Immunologic or Allergic Disorders

Vasculitis syndromes

Castleman disease

Kimura disease

Bee sting

Food allergens

Serum sickness

+Associated With Malignant Disease

Lymphoma

Leukemia

Solid tumors

+**Glomerular Hyperfiltration**

Oligomeganephronia

Morbid obesity

Adaptation to nephron reduction

PATHOGENESIS

` Glomerular capillaries are lined by fenestrated endothelium which in turn rests on glomerular basement membrane which in turn is covered by glomerular epithelium also known as podocytes[3]. Neighboring podocyte foot processes are covered by cellular extensions called foot processes .These structures form the glomerular filtration barrier.

Nephrotic syndrome can occur as a result of either structural or functional loss of the glomerular filtration membrane.Patients with Idiopathic Nephrotic syndrome[6] show a break down in the charge selective barrier to filtration resulting in massive proteinuria, whereas in

genetically determined SRNS, it is the structural alterations in the podocytes due to gene mutations which pay a mojor role in pathogenesis of the disease.

The exact cause of breakdown of the filtration barrier in idiopathic NS is still not known although there are certain hypotheisis regarding it like

+dysregulation of T cell function

Provoked by infection,allergen,vaccine, lymphoma etc.

Proteinuria resolving after treatment with immunosuppressive therapy supports this theory.

+damage to glomeular filtration barrier due to some soluble factors

As evidenced by relapse in some patients with FSGS after transplant.

PATHOPHYSIOLOGY1.2,3

HYPOALBUNIMIA

Due to the massive urinary protein loss and due to catabolism of proteins in renal tubules

HYPERTRIGLYCERIDEMIA AND HYPERCHOLESTREMIA

This occurs due to the stimulation of the hepatic protein synthesis due to hypoalbuinimia which includes increased production of lipoproteins.

THROMBOSIS

This occurs due to the increased hepatic synthesis of proteins as a result of hypoalbminimia. Increased levels of fators 1,5,7,8,10 and 13 occurs . There is also a decrease in levels of antithrombin 3,protein C and S as a result of renal protein losses.The increases hematocrit as a result of severe volume contraction also results in a hypercoagulable state.

INFECTIONS

Increased risk of infections in Nephrotic syndrome are as a result of decreased levels of serum IgG due to urinary loss as well as due to increased levels of serum cholesterol.

Use of immunosuppressive drugs further increase the chances of infection.

RENAL FAILURE

Renal failure occurs rarely in Idiopathic NS.When it occurs, it is due to acute tubular necrosis due to severe volume contraction or due to bilateral renal vein thrombosis.

Chronic renal failure is a part of disease process in SRNS due to persistently occurring proteinuria over a long period of time.

EDEMA

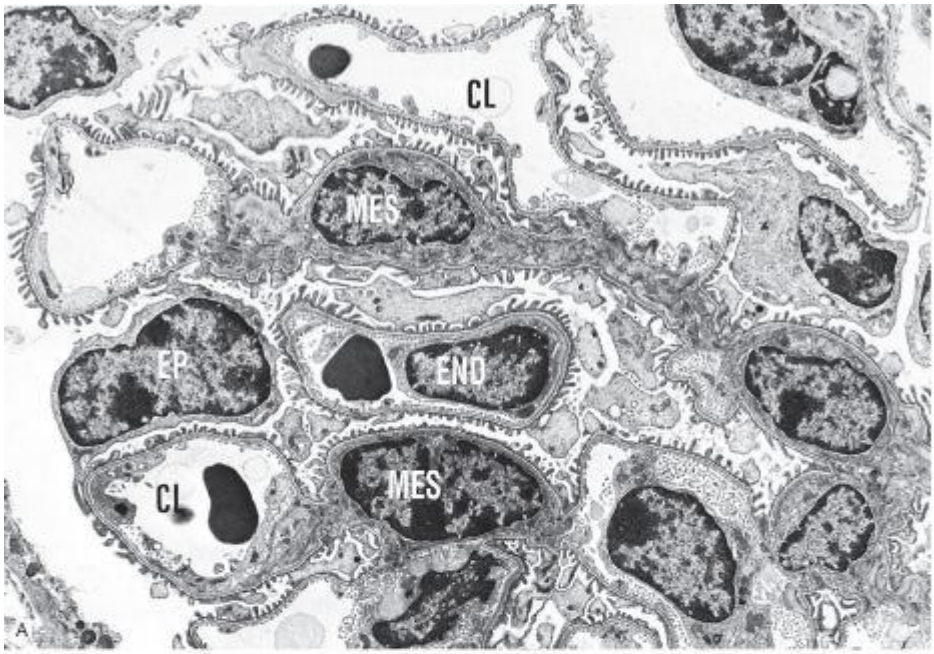
Decreased oncotic pressure due to decreased plasma albumin leads to movement of fluid from the vascular system to the interstitial space. Hypoalbuminia and decreased oncotic pressure also trigger sodium retention via rennin-angiotensin-aldosterone axis(underfill theory)[11] and via the increased activation of ENaC channels in the collecting tubules(overfill theory).

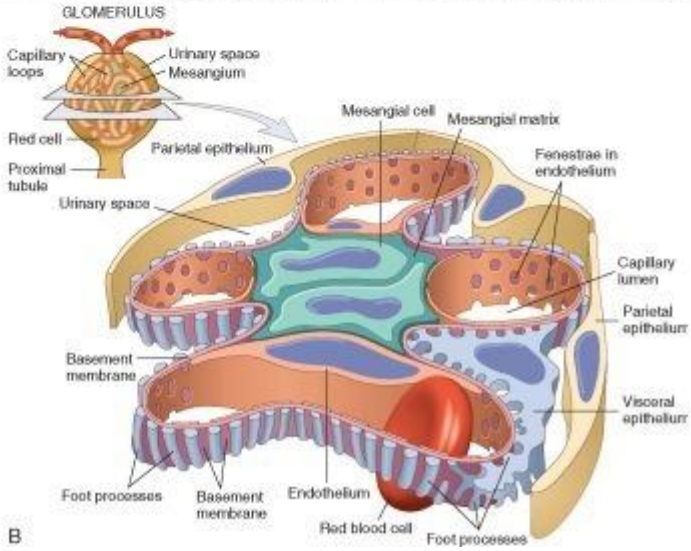
In a subset of patients due to underfill, there have been reported states of hypovolemia inspite of peripheral edema.These patients due to there decreased intravascular volume are at an increased risk for developing thrombotic complications like renal vein thrombosis,deep venous thrombosis,pulmonary and cerebral vein thrombosis, IVC thrombosis and acute tubular necrosis due to volume depletion.

In another subsetof patients,due to incrased activation of ENaC channels in collecting tubules there is sodium retention which causes water retention along with it which is the cause for edema.

PATHOLOGY

Normal glomerular filtration membrane





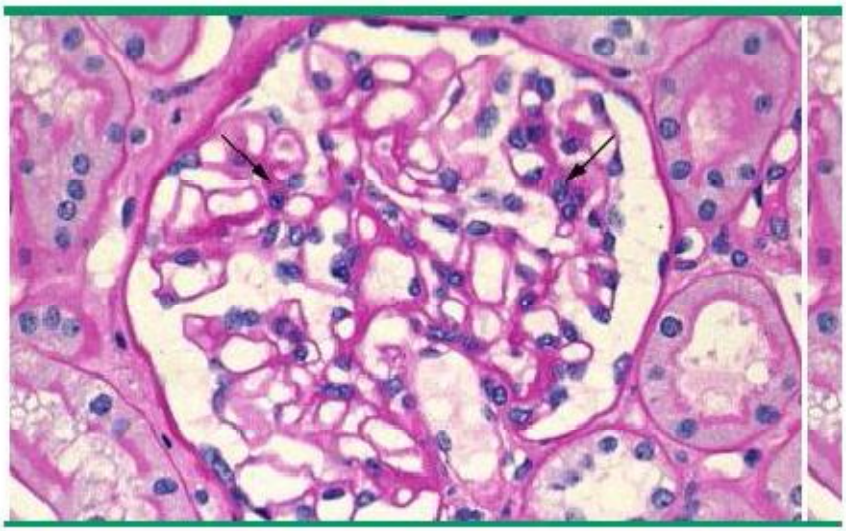
MINIMAL CHANGE GLOMERULAR DISEASE [2,18]

Light microscopy-normal or mild increase in mesangial cellularity and matrix.

Immunofuurosence-negative for immune deposits.

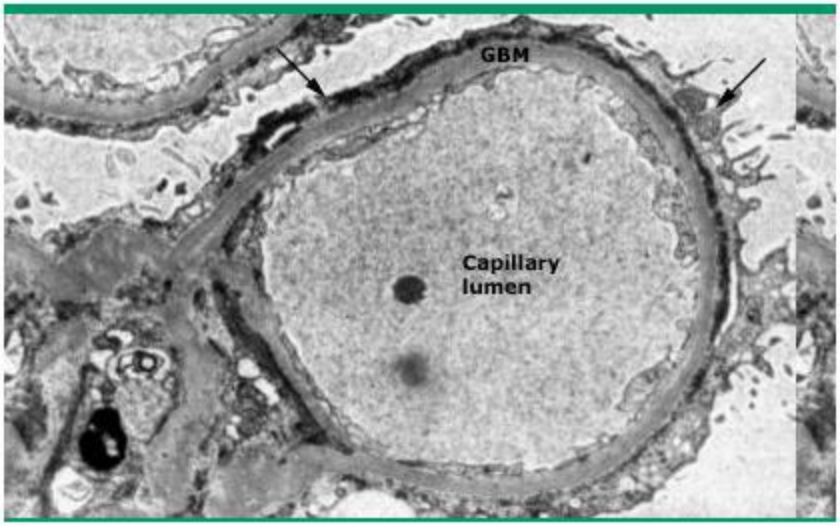
Electron microscopy-fusion of foot process

Light microscopy in minimal change disease

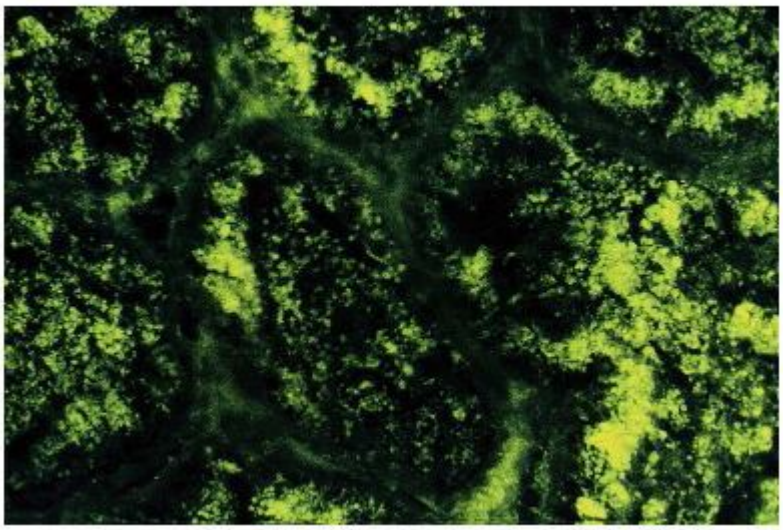


Light micrograph of an essentially normal glomerulus in minimal change disease. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary walls is normal, and there is neither expansion nor hypercellularity in the mesangial areas in the central or stalk regions of the tuft (arrows).
Courtesy of Helmut G Rennke.

Electron microscopy in minimal change disease



Electron micrograph in minimal change disease showing a normal glomerular basement membrane (GBM), no immune deposits, and the characteristic widespread fusion of the epithelial cell foot processes (arrows).
Courtesy of Helmut Rennke, MD.



Immunofluorescence preparation demonstrating numerous lipid droplets in the proximal tubular epithelial cells.

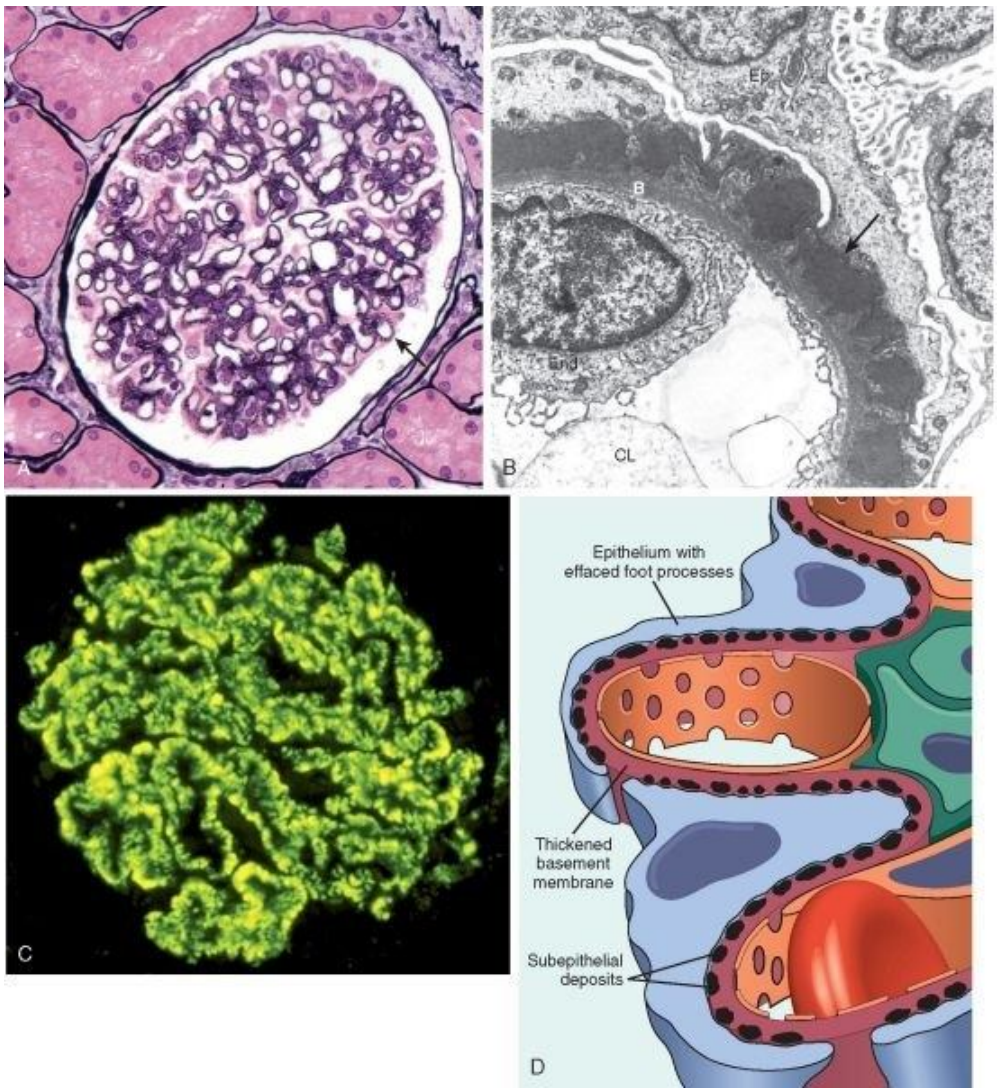
DIFUSE MESANGIAL PROLIFERATION

Light microscopy-diffuse increase in mesangial cellularity and matrix.

Immunofuurosence-trace to 1+ of IgM or IgA or C3 deposits in the mesangium.

Electron microscopy-fusion of foot processs along with diffuse proliferation of mesangial cells and matrix.

Diffuse mesangial proliferation



FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

Light microscopy-focal(some but not all glomeruli involved) and segmental(part of glomerular tuft involved) sclerosis and mesangial proliferation.

Immunofuurosence-IgM and C3 deposits in areas of sclerosis.

Electron microscopy-obliteration of capillary lumen in tuft having segmental sclerosis while the non involved segment has fusion of foot processes.

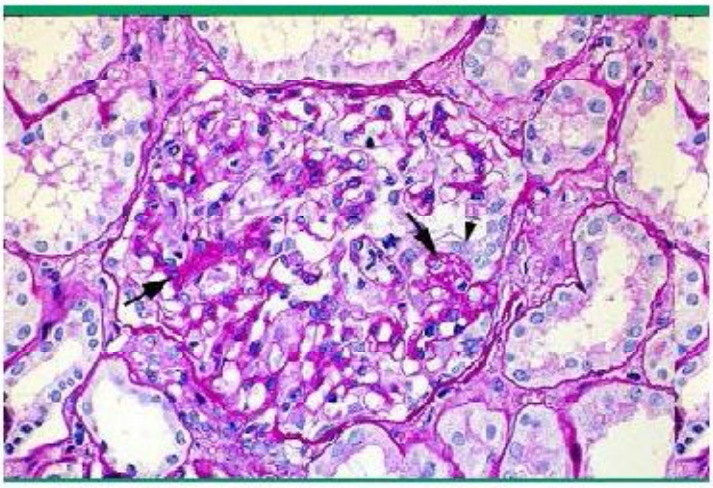
There are 5 histological variants of FSGS

-FSGS not otherwise specified.

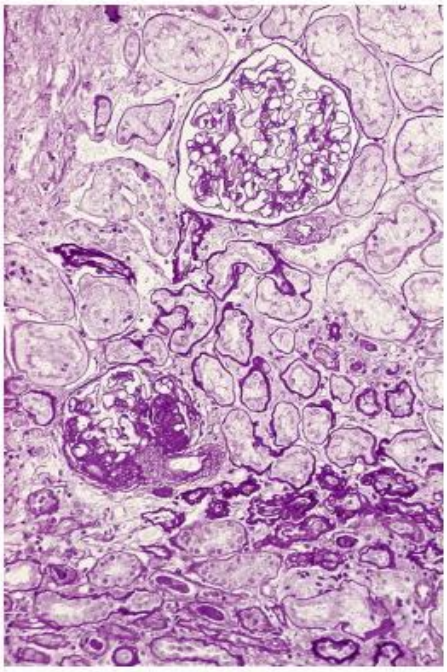
-collapsing variant:found in patients with HIV,parvo virus infection;worst prognosis

-perihilar,cellular and tip variants.

Mild FGS

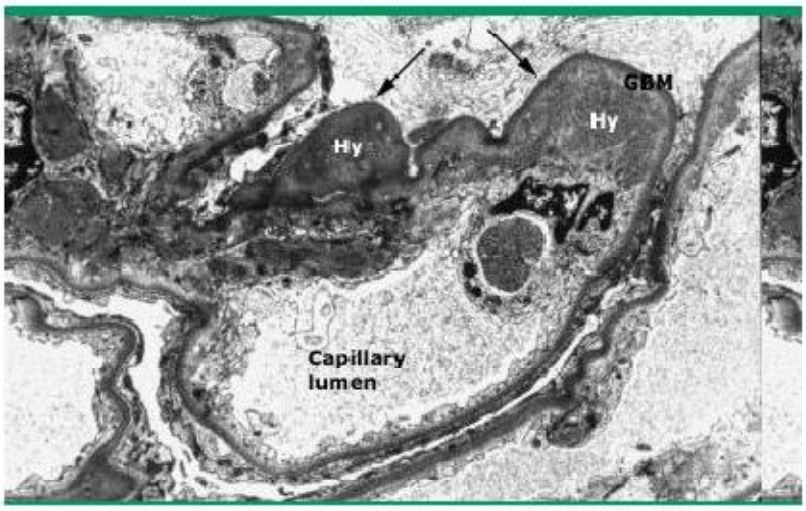


Light micrograph shows early changes in focal glomerulosclerosis with segmental capillary collapse (arrows) in areas of epithelial cell injury (small arrowhead).
Courtesy of Helmut Rennke, MD.



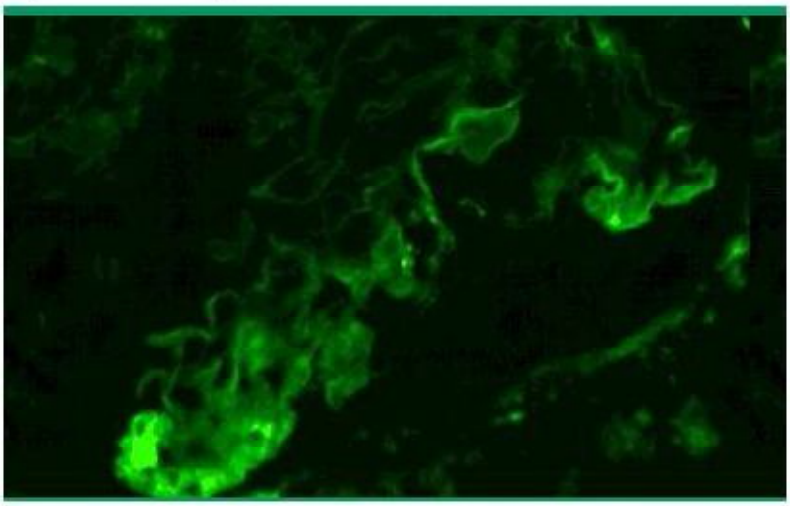
Biopsy from a patient with focal and segmental glomerulosclerosis. One of the glomeruli shows segmental sclerosis, while the other appears unremarkable. Tubular atrophy is also seen.

Focal glomerulosclerosis



Electron micrograph in focal segmental glomerulosclerosis shows diffuse epithelial cell foot process fusion with occasional loss of the epithelial cells (arrows). The other major finding is massive subendothelial hyaline deposits (Hy) under the glomerular basement membrane (GBM). These deposits reflect insudation of plasma proteins, not the deposition of immunoglobulins. These deposits contribute to narrowing of the capillary lumens.
Courtesy of Helmut Rennke, MD.

IgM in focal glomerulosclerosis



Immunofluorescence microscopy in focal segmental glomerulosclerosis is usually negative, except for probably nonspecific deposition of IgM in sclerotic area at the bottom of the glomerulus.
Courtesy of Helmut Rennke, MD.

MCD r DMP WITH IgM DEPOITS IN THE MESANGIUM

In addition to the LM and EM findings of MCD or DMP, there are deposits of IgM in the mesangium.

Such patients usually respond very poorly to steroids.

CLINICAL FEATURES[1,2,6]

The typical age group for occurrence of nephrotic syndrome is pre school age group. The patient presents with insidious onset facial puffiness more on awakening followed by slowly progressing generalised edema which may be associated with oliguria. There may be a history of preceeding respiratory or viral infections which may act as a trigger for

nephrotic syndrome. Some may present with features of severe edema like labial or scrotal edema,respiratory compromise due to massive ascites. Occassionally patients may present with diarrhea due to bowel wall edema. Sometimes rarely the patient may present critically ill due to peritonitis,bacteremia, pnuemonia or with thrombotic episodes. Some may have symptoms of hypotension like abdominal pain,persistent vomiting,dizziness and cold extremities. These symptoms are due to decreased intravascular volume[11,21,27].

On physical examination, the extent of edema must be assessed. A careful examination must be done to look for any underlying infections like Urinary tract infections,pneumonia,peritonitis. Blood pressure must be monitored along with urine output. Small and large joints must be checked for any signs of inflammation or restriction of movements which may indicate any collage vascular disorder. A search for any organomegaly must be made which may indicate any underlying disorder which can cause secondary nephrotic syndrome.

Facial puffiness-one of the initial symptoms of NS

Scrotal edema and ascites in a patient before and after treatment

Pitting pedal edema

Patient with massive edema-with both periorbital puffiness and massive ascites

Frothy urine in a patient with nephrotic syndrome

LABORATORY EVALUVATION

INVESTIGATIONS TO CONFIRM THE DIAGNOSIS[1,7,12]

Urine analysis of the early morning first samle to look for proteinuria and urine spot PCR, blood urea creatinine and serum electrolytes,serum triglyceride and cholesterol levels,serum albmin,urine electrolytes and FeNa and fractionalurinaryexcretion of potassium to determine the intravascular status .

INVESTIGATIONS TO RULE OUT INFECTIONS

Urine culture to rule urinary tract infection,complete blood counts and CRP to rule out any infections,Mantoux and chest xray to rule out tuberculosis.

OTHER INVESTIGATIONS WHICH AY BE NEEDED AT TIMES

USG abdomen to rule out renal anomalies ,Anti nuclear antibody levels ,renal biopsy if the child is above 10 yrs of age.ASO and C3 levels if there is microscopic hematuria in urine microscopy.

Indications for biopsy in nephrotic syndrome

-age of onset< 1yr or >10 yrs.

-gross hematuria,persistent microscopic hematuria or low serum C3.

-sustained hypertension.

-renal failure not attributable to hypovolemia.

-after initial treatment-

+Proteinuria persisting after 8 weeks of full dose steroid therapy(labeled as SRNS)

+Before starting cyclosporine or tacrolimus.

+After 2 yrs of therapy with calcineurin inhibitors to check for toxicity.

MANAGEMENT

SYPMTOMATIC AND SUPPORTIVE MANAGEMENT[1,2,7,8,12]

Any child with massive edema,fever,unstable vital signs,urine outout<0.5 ml.kg/hr and severe hemoconcentration as suggested by a hematocrit more than 48% must be hospitalized. Fluid intake and output, blood pressure and daily weight charts must be maintained.

+ Dietary management

The child should be placed on “no added” salt regimen i.e 1 to1.5 gms of salt per day. Fluid restriction will be needed. Patients with severe edema -insensible water loss of previous day,moderate edema-insensible water loss with previous day urine output,mild edema-mild or no fluid restricton.

Daily recommended allowences of protein are allowed of which 2/3 rd must be first class proteins like egg albumin.

+Diuretics

Diuretics are useful in children with moderate to severe edema with oliguria. Intravascular volume status must be assessed with FeNa and fractional ppotassium excretion in urine prior to the use of diuretics in order to prevent the aggrevation of intravascular depletion which may

cause episodes of thrombosis and acute tubular necrosis. Furosimide is the most commonly used diuretic in a dose of 1-2 mg/kg/day either orally or intravenously. Other diuretics like thiazide diuretics,spirinalactone, metalazone etc may also be used. Metalazone is especially useful in refractory edema,usually in refractory nephrotic syndromes. Diuretics like metalazone are used half hour prior to the administration of furosimide for maximal effect. Serum levels of potassium must be monitored while using diuretics due to their propensity to cause hypokalemia. In paients with intravascular volume contracted states, injection human albumin in doses of 1 gm/kg/day over 4hrs may be used to improve intravascular status and mobilize the edema. Fresh frozen plasma in doses of 10 ml/kg/day over 4hrs may also be used in case of non availability of human albumin. Human albumin/Fresh frozen plasma may also be used is patients with severe edema causing respiratory compromise along with diuretics like furosimide to decrease edema in better way.

+control of any infections like urinary tract infections ,pneumonia ,peritonitis etc before the start of steroids.

+Specific therapy[1,7,8]

The main aim of therapy is to induce and maintain remission in active nephrotic syndrome while minimizing the side effects due to drugs most of which are immunesuppresants.

-Steroids-these are the mainstay of therapy in newly diagnosed cases of nephrotic syndrome. APN regimen for steroids is the one used in ICH and HC. It consists of 2mg/kg/day dose of prednisolone given daily for 6 weeks followed by 1.5 mg/kg/day every other day for another 6 weeks followed by tapering of steroids over 2 weeks. In patients with infrequent relapse, 2 mg/kg/day prednisolone is given daily till remission is achieved and then it is followed by 1.5 mg/kg/day every other day for a period of 4 weeks. In patients with frequent relapse or steroid dependent nephrotic syndrome, a low dose steroid is given at a dose of 0.25-0.75 mg/kg/day every other day for a period of 6-18months. If the patient needs more doses of steroids or develops side effects due to steroids, then alternate durgs are introduced.

-Other immunomodulators-

Steroid dependent nephrotic syndrome or frequent relapse[9,10,13]

In ICH and HC pulse dose of cyclophospamide is used in dose of 500 mg/m2 given once a month for a duration of 6 months. Other drugs that are used in SDNS/FRNS are levamisole, oral cyclophospamide and mycophenolate mofetil in refractory cases.

Steroid resistant nephrotic syndrome[15,16,17,19]

In our hospital a trial of high dose steroids in the form of pulse methyl prednisolone is given in Mendosa Regimen[17]. This is followed by use of drugs like Tacrolimus ,cyclosporine, a combination of tacrolimus and mycophenolate mofetil[19] etc if the patient is not responding to Mendosa regimen. If the patient is still not in remission ,then antiproteinuric measures like angiotensin receptor blockrs or AT1 antagonists[15] along with antihypertensives are used to control proteinuria and hypertension.

+Vaccination-

Patients with nephrotic syndrome have unusual susceptibility to pneumococcal infection. Hence IAP recommends the use of 2-4 doses of heptavalent pneumococcal conjugate vaccine for children below 2 yrs with nephrotic syndrome. For children between 2-5 yrs , 1 dose of heptavalent followed by 1 dose of 23 valent vaccine is recommended 8 weeks after the first vaccine.

SUMMARY AND CONCLUSIONS

Nephrotic syndrome is a common disease in children especially in preschool age group. It is a disease which mainly presents with edema,oliguria which are insidious in onset which may or may not be associated with hematuria. There are a multitude of reasons which can cause nephrotic syndrome among which idiopathic nephrotic syndrome is the commonest form. In patients with nephrotic syndrome the intravascular status can be hypo or hypervolemic despite massive edema[11,21,27]. The signs of volume depletion can be subtle and not very much clinically apparent. This can be aggrevated by inadvertent use of diuretics to mobilize edema which may lead to thrombotic complications like renal vein, pulmonary, cereberal thrombosis or acute tubular necrosis which all can be life threatening. Hence it is prudent to measure intravascular volume status before instituting the use of diuretics to mobilize edema in a patient with nephrotic syndrome.

INTRAVASCULAR VOLUME STATUS IN FIRST EPISODE NEPHROTIC SYNDROME

INTRODUCTION AND NEED FOR THE STUDY

Nephrotic syndrome is a common disease in children especially in preschool age group. It is a disease which mainly presents with edema,oliguria which are insidious in onset which may or may not be associated with hematuria. In patients with nephrotic syndrome the intravascular status can be hypovolemic or hypervolemic despite massive edema. The signs of volume depletion can be subtle and not very much clinically apparent. Volume depletion in patients with nephrotic syndrome can present with symptoms like giddiness,abdominal pain vomiting etc. which can be very subtle in children or which may not be reported at all. Diuretics are the most common drugs used to treat edema in nephrotic syndrome. This state of hypovolemia can be aggrevated by inadvertent use of diuretics to mobilize edema which may lead to thrombotic complications like renal vein, pulmonary, cereberal thrombosis or acute tubular necrosis which all can be life threatening. Hence it is prudent to measure intravascular volume status before

instituting the use of diuretics to mobilize edema in a patient with nephrotic syndrome.

AIM OF THE STUDY

To study and assess the intravascular volume status in 1st episode Nephrotic Syndrome and determine if the patient is hypovolemic or hypervolemic to determine the safety of use of diuretics to decrease edema in patients with 1 st episode nephrotic syndrome.

METHODOLOGY

PLACE OF STUDY

General pediatric medical wards of a tertiary care referral government hospital-Institute of Child Health and Hospital for Children.

STUDY DESIGN

Prospective observational study

DURATION OF STUDY

January 2015 to September 2015

STUDY POPULATION

Suspected patients with first episode of Nephrotic syndrome.

INCLUSION CRITERIA

Children with

- Proteinuria >50 mg/kg/day or spot PCR >2 or urine dipstick 2+ or more.
- Serum albumin< 2.5 g/dl.
- Serum cholesterol>200 mg/dl.

EXCLUSION CRITERIA

- Previous episodes of nephrotic syndrome.
- Prior use of diuretics for edema during the present episode.

ETHICAL ISSUES

- Routine blood investigations were sent for the patients from general ward for the patients from which the necessary results were collected.
- The necessary urine results were also collected from the routine urine tests samples sent from ward for patients under evaluation for suspected nephrotic syndrome.
- Institute ethical committee approval was obtained before the commencement of the study.
- Informed consent from the patient’s paterts was obtained before voluntary enrolment into the study.

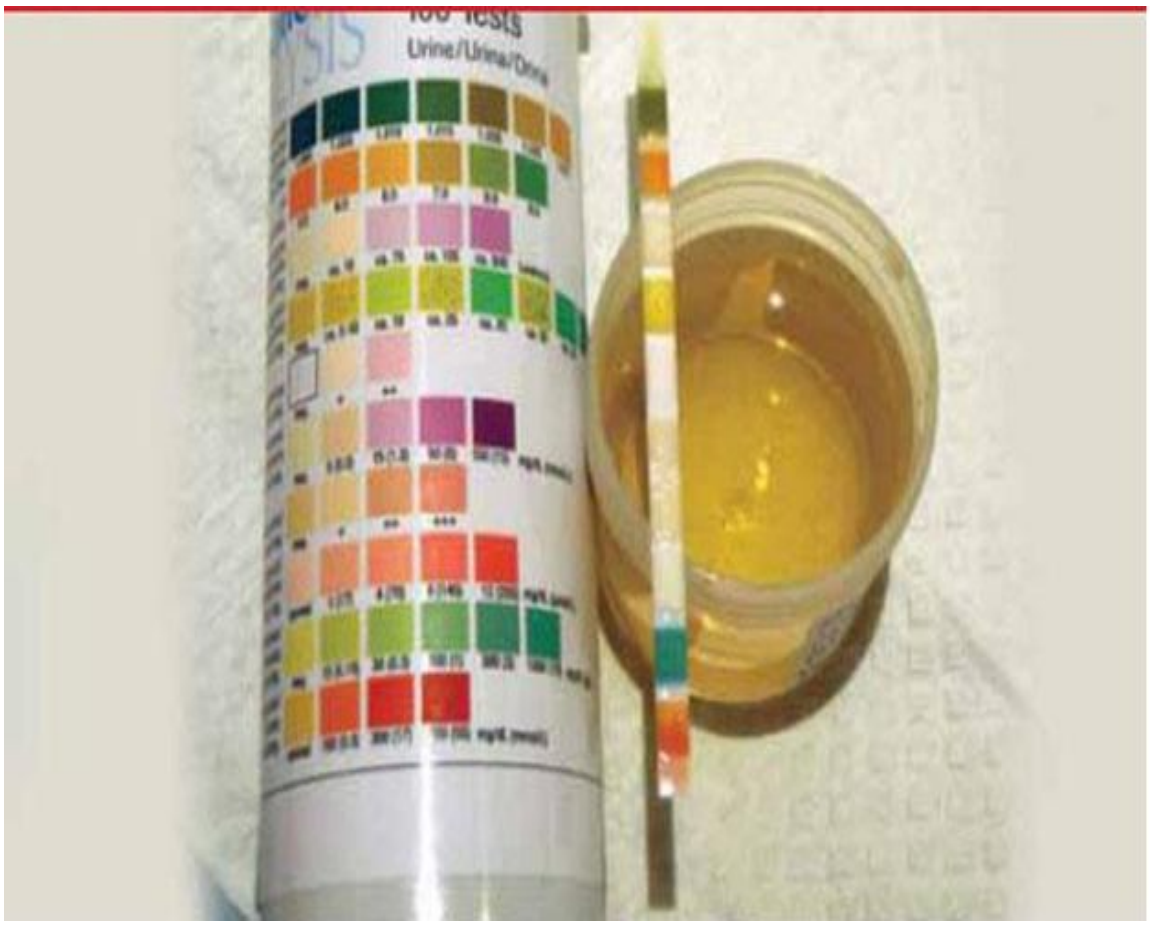
STUDY MANEUVRE

All the general pediatric medical wards were informed about the study with a circular explaining the study in short, inclusion criteria for enrollment, exclusion criteria and information for informed consent and about how to obtain the sample. Informed consent was obtained from the patents before enrollment into the study. Blood samples were obtained with aseptic measures following universal precautions in plain test tube(red) provided for the purpose. First morning urine samples were collected in plain urine bottles after washing the perineum with soap. Both the urine and blood samples were sent to biochemistry laboratory without delay for analysis. The patients were next taken to Department of Cardiology for echocardiogram to measure the IVC collapsibility index. All the testing were done after ensuring that diuretics were not given to the patient to decrease edema during this episode of nephrotic syndrome.

Test tubes used to collect blood samples.

Plain bottles used for urine collection.

Dipstick to detect proteinuria



SAMPLE ANALYSIS

All the samples were sent to biochemistry laboratory without delay. They were analyzed by skilled technician in the biochemistry laboratory. The testing was done using the following methods using Erba Manihier EM 200 auto analyzer-

+Serum sodium and potassium-using ion electrode method.

+serum creatinine-jaffe’s kinetic method.

+serum proteins- biuret method

+serum albumin- brome cresol green reagent method measured by colorimetric method.

+urine analysis

Diluents used-company specified diluents diluted in the ratio of 1:10

+urine sodium and potassium- ion electrode method.

+urine creatinine- jaffe’s kinetic method.

+urine protein-sulphosalycilic acid method measured by colorimetric method.

Erba Manihier EM 200 auto analyzer used for analysis of blood and urine samples.

From the above values FeNa and Relative urinary potassium excretion

will be calculated using the given formulae.

- FeNa- UNa X PCr X 100/PNa X UCr
- Fractional urinary excretion of potassium-Uk/Uk+UNa)

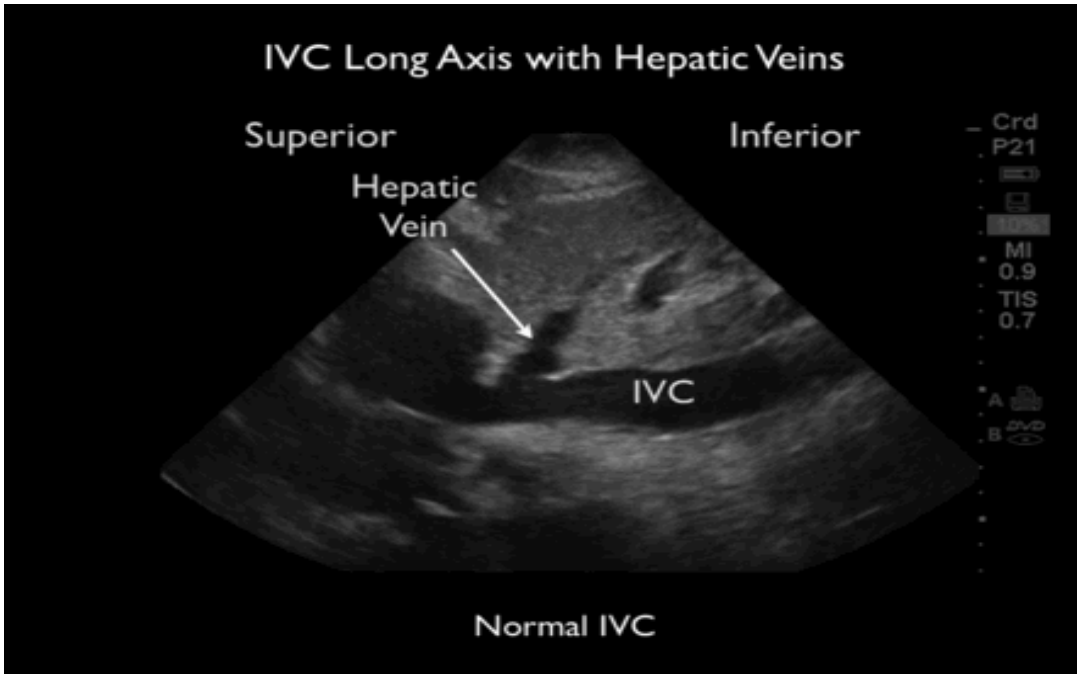
IVC COLLAPSIBILITY INDEX

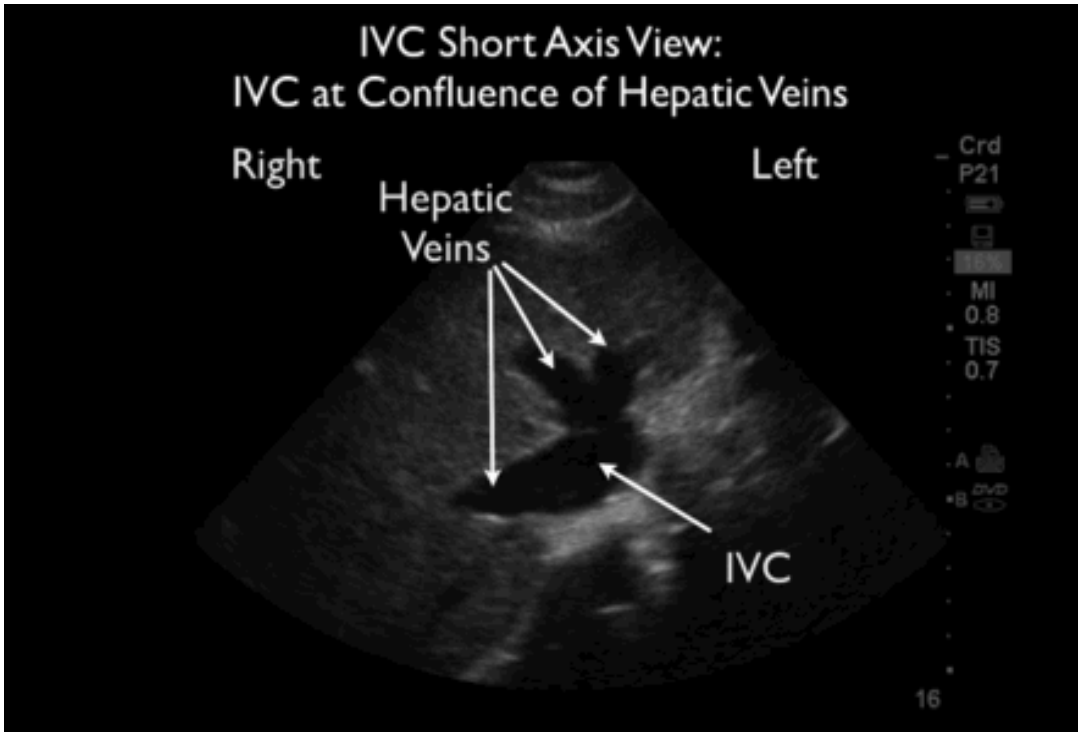
IVC collapsibility index was measured using echocardiography in Pediatric Cardiology department by trained cardiologist using the following given method.

To image the IVC, the probe was placed in the subxiphoid 4-chamber position with the probe marker oriented laterally in order to identify the right ventricle and right atrium. Then the probe is progressively aimed toward the spinal column, where the convergence of the IVC with the right atrium can be seen. The IVC is then followed inferiorly, specifically looking for the confluence of the hepatic veins with the IVC . The IVC was evaluated in the long-axis plane. For this view, the probe was turned from a 4-chamber subxiphoid into a 2-chamber subxiphoid orientation, with the probe now aligned in a longitudinal orientation . Though this view allows visualization of the IVC throughout the length of the hepatic segment, there is a possibility that the true size of the IVC may be underestimated in the long axis due to a common error which known as the cylinder tangent effect. This effect tends to occurs when the ultrasound beam travels via the vessel longitudinally through an off-centered plane. One of ways to avoid underestimating the size of the IVC was to angle the probe slightly laterally and medially until the greatest

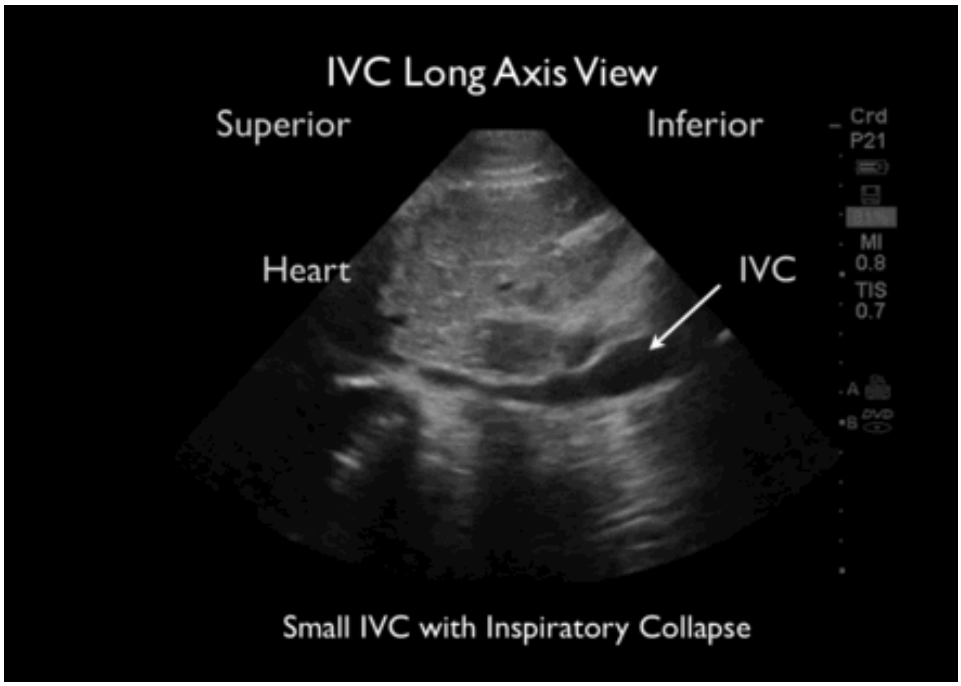
dimensions of IVC are identified. The diameter of the IVC was then measured perpendicular to the long axis of the IVC at end-expiration and end-inspiration. The finding of an IVC with large inspiratory collapse (high caval index) is suggestive of with low volume states.

Echo views of IVC

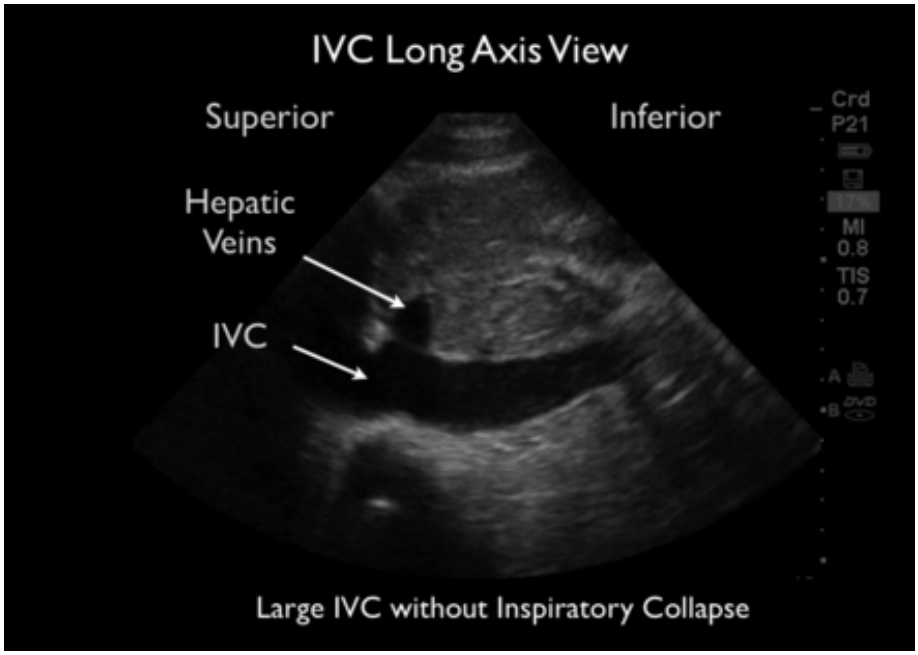




Echo view of IVC in volume contracted state



IVC in hypervolemic state



IVC collapsibility index will be calculated using the following formula-

(IVC dia exp- IVC dia insp)/ IVC dia exp

From the above values, hypovolemic status will be defined as

- FENa<1 and
- Uk/Uk+Una>60% and
- IVC collapsibility > 50 %

The patients not satisfying the above criteria will be classified as having a hypervolemic intravascular status.

REVIEW OF LITERATURE

Historical overview

The term “nephrosis” was coined in the beginning of the 20th century, it was characterized by proliferation and exudation of inflammatory cells. Since then, “nephrotic syndrome” was the term used to refer a group of similar and related diseases mainly of the kidney.

The initial records of nephrotic syndrome can be traced back to beginning of this era. In the times of old Alexandria, it was thought that urine was produced in kidneys.

☐ The old saying from Hippocrates was “Bubbles floating upon the surface of the urine denote affection of the kidneys, and the disease will be long drawn”.

☐ In the mid 18th century(1764), Cotungo, first described massive edema in a soldier whose urine was later found to be heat coagulable.

☐ In the 19th century (1836), proteinuria was noted in some renal diseases in patients with the presence of edema by Bright, Glomerulonephritis was known as Bright’s disease for about a century.

☐ In 1905, Fredrick Muller was the one who first used the term “Nephrosis” to distinguish a subset of renal disorders. Initially, it was thought that tubules were the source for the protein leak.

Glomeruli were later found to be the cause of protein leak finally in the 1940s.

☐ Munk, in 1913, found the association of nephrosis and lipoid droplets in the urinary sediments in nephrosis patients and coined the phrase lipoid nephrosis.

☐ To describe patients with proteinuria, edema and hyperlipidemia, Clovin and Goldberg started using the terminology “Nephrotic Syndrome”.

☐ As a treatment of nephrotic syndrome,Synthetic steroid hormones (prednisone, glucocorticoid prodrug) were used since 1950. Schering and Cepjohn, in 1955, started using prednisolone.

STUDIES RELATED TO MY TOPIC

1. **Urinary indices in nephrotic syndrome**

Published –Indian journal of nephrology,jul-sep 2011

Authors- M. Sahay et al . Osmania medical college ,Hyderabad

Aim-Children with Nephrotic syndrome with edema may have variable intravascular volume status- hypo, hyper or normovolemic status. Clinically it is very difficult to determine the volume status. Hence urinary indices may be used to determine the volume status in children with nephrotic syndrome.

Study design-prospective observational study.

Result and conclusion-measurements of urinary indices are simple bedside tools to measure the intravascular status in children with nephrotic syndrome. Children with low urinary sodium excretion with high potassium excretion were found to be hypovolemic and needed volume expansion before use of diuretics. Whereas children with FeNa >0.2 and frac potassium excretion > 60% were found to be hypervolemic and the use of diuretics was found to be safe in them.

2. Pathogenesis of edema formation in the nephrotic syndrome

Published –Journal of ped nephrology,March 2001 vol 16

Authors- JGJ Vande walle ,Docknerwolke et al.

Result and conclusion- A total 110 children with nephrotic syndrome were studied. Based on the observation from the study, the pathogenesis of edema formation were redefined. The basic defect was identified to be faulty excretion by the kidneys. It was found out that functional hypovolemia was found to be associated depending upon the stage in the development of the NS, the rate of progression in the development of hypoproteinemia, and the absolute levels of plasma oncotic pressure. This applied equally to Minimal lesion NS as well as NS with significant histological lesions. Hypovolemia had therapeutic implications. A quick bedside assessment of hypovolemia was made using FeNa and fractional excretion of potassium in urine.

3. Inferior vena cava indices determine volume load in minimal lesion nephrotic syndrome.

Authors-Osman Dönmez, Sevgi Mir, Ruhi Özyürek, Alphan Cura , Caner Kabasakal et al.

Published-Pediatric nephrology, march 2001 vol 16

Study method- a total of 12 children with minimal lesion NS were studied. They were divided into 3 stages- stage A: edematous; stage B: 50% decrease in weight gain; stage C: edema free. The ideal weight of all patients in stage A was found to be more than the ideal weights . Serum total protein, albumin and urine sodium levels were also found to be low in these patients.IVC indices to determine the volume load were suggestive of hypovolemia in these patients. Plasma rennin activity in these patients were found to be significantly different from controls in stage A. PRA and serum aldosterone levels were found to be not different in those in stage B from the control group. However, the increase in PRA was found to be significant in stage C. Although there was a significant weight decrease in stages B and C, it had no effect on IVCI, LAD, and cardiothoracic index.

Result and conclusion- IVCI, IVCCI, and LAD measurements by echocardiography (ECHO)were found to be easy and reliable methods to assess the intravascular volume load in patients with Minimal lesion NS.

4. Caval Sonography in Shock-A Noninvasive Method for Evaluating Intravascular Volume in Critically Ill Patients

Authors- Dina Seif, MD, MBA, RDMS⇓, Thomas Mailhot, MD, RDMS, Phillips Perera, MD, RDMS and Diku Mandavia, MD et al

Published- Journal of Ultrasound in Medicine December 1, 2012 vol. 31no. 12 1885-1890

Aim- to determine the intravascular volume in critically ill patients with shock with the help of bedside ultrasoography.

Methods-IVC collapsibility indices measured from 2 axis- short axis and long axis were used to measure the volume status in critically ill patients with shock in the ICU to guide in resuciation.

Results and conclusion- Decreased dilatation of the IVC following a fluid challenge was found to be more sensitive than blood pressure in the identification of hypovolemia in trauma patients. IVC sonography with dilation and decreased collapsibility rapidly identifies patients with congestive heart failure and volume overload. More than a single measurement of the IVC, it will be more useful to measure the changes in vessel size and collapsibility over time in response to breathing cycle and in response to an intervention.

Pitfalls- One single long-axis view may not be accurate, hence it is recommended to measure the IVC volume in both short and long axes. Inferior vena cava indices measurements should be made at or near the junction with hepatic veins. Measurements at other places may not reflect the actual intravascular volume status. Interpretation of IVC indices is improper in conditions that restrict the physiologic variability of the IVC, like liver cirrhosis, fibrosis, masses causing external compression of IVC and in conditions with elevated intra-abdominal pressure.

5. Treatment of Severe Edema in Children with Nephrotic Syndrome with Diuretics Alone — A Prospective Study

Authors-Gaurav kapur, Rudolph valentine et al.

Aim- Severe edema in patients with nephrotic syndrome (NS) can be associated with volume contraction or volume expansion . Normally, severe edema is treated with intravenous albumin and diuretics, which is appropriate management for VC patients. But in VE patients, this can result in volume overload. The aim of this study was to evaluate the management of severe edema in NS with diuretics alone.

Methodology - 30 NS patients having severe edema were enrolled into this study in two phases. VC was determined based on fractional excretion of sodium (FeNa) <1%. Patients identified with VC received IV albumin and furosemide. VE patients were treated with intravenous furosemide and oral spironolactone. Volume contraction was redefined as FeNa <0.2 n phase 2 of this study and then this newly defined patients received the treatment protocol described above.

Results and conclusion- In pediatric patients with NS, with FeNa >0.2, diuretic therapy alone is safe whereas in patients with FeNa <0.2 , IV albumin with diuretics was preferred.

6. Pathogenesis of edema formation in the nephrotic syndrome.

Authors-Palmer BF,Alpen RJ et al.

Published-kidney international supplement [1997, 59:S21-7]

Type- journal article,review.

Results- The development of edema in the nephrotic syndrome has been thought of as an underfill mechanism. According to this theory, albuminuria results in hypoalbuminemia and reduced plasma oncotic pressure. As a result of which plasma fluid translocates out of the intravascular space and leads to a decrease in intravascular volume status. In response to this underfilled circulation, compensatory mechanisms are then activated that lead the kidney to retain salt and water. While an underfill mechanism may be responsible for edema formation in a small minority of patients, recent findings suggest that edema formation in most of the nephrotic patients is as a result of primary salt retention. Direct measurements of blood and plasma volume or measurement of neurohumoral markers that can indirectly reflect circulatory volume are mostly consistent with a state of either euvolemia or a state of hypervolemia. The intrarenal mechanisms responsible for primary sodium retention is not fully elucidated, but may involve tubular unresponsiveness to natriuretic effect of atrial natriuretic peptide.

7. **Hypo- and hypervolemic edema in children with steroid sensitive nephrotic syndrome**

Authors-Mehmet Akif BÜYÜKAVCI , Mahmut ÇİVİLİBAL, Murat ELEVLİ , Hatice Nilgün SELÇUK DURU

Published-Turkish journal of medical sciences,jan 2015

Materials and methods: 32 Steroid sensitive NS patients and 30 healthy children were taken in this study. The intravascular volume status of patients were studied by clinical and laboratory parameters, like fractional sodium excretion (FENa) and distal sodium/potassium exchange (UK/UNa+K ratio). Inferior vena cava collapsibility index (IVCCI), left atrial diameter (LAD), aortic diameter (AD), and left ventricular mass index (LVMI) were measured using echocardiographic methods.

Results: While evaluating the volume status of patients, 8 patients (25%) were found to be hypovolemic while the rest 24 patients (75%) were nonhypovolemic (normovolemic or hypervolemic). LAD was decreased in hypovolemic patients.

Conclusion: The majority of patients with Steroid Sensitive NS are normovolemic or hypervolemic and echocardiography is an easy and noninvasive method for the evaluation of volume status in these patients.

RESULTS

RESULTS AND ANALYSIS

The results were entered in an excel sheet and were analyzed using open epi version 2.3.1 for statistics.

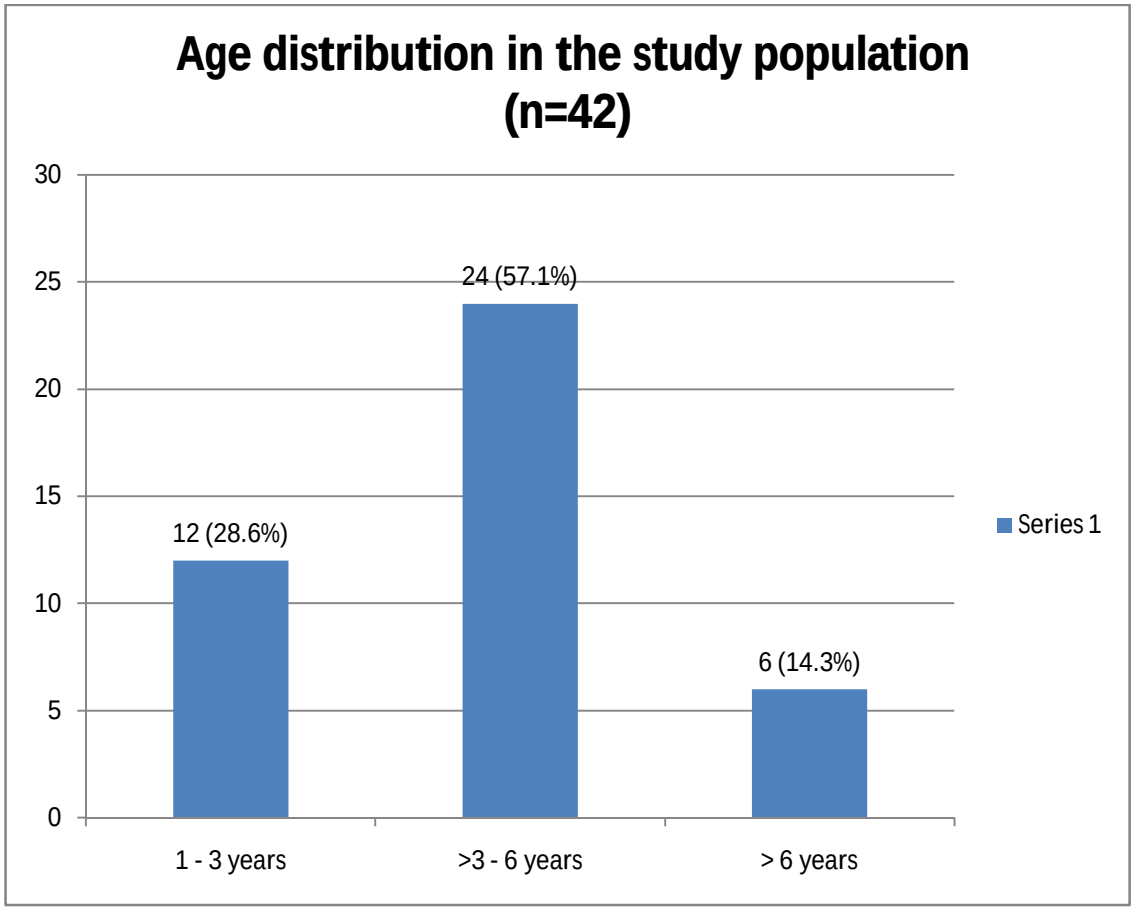
A total of 42 patients were included in the study who satisfied the inclusion criteria.

AGE DISTRIBUTION

The variation in age among the patients was from 1 yr to 10 yrs. Among the 42 children, 12 (28.6%) were in the age group between 1 to 3 years. There were 24(57.1%) children in the age group between 3 and 6 years which forms the largest age group in this study. There were 6 (14.3%) children of age more than 6 years and less than 10 years.

Age distribution of patients in this study

Age group	Frequency	Percentage
1-3 yrs	12	28.6
3-6 yrs	24	57.1
6-10 yrs	6	14.3
Total	42	100

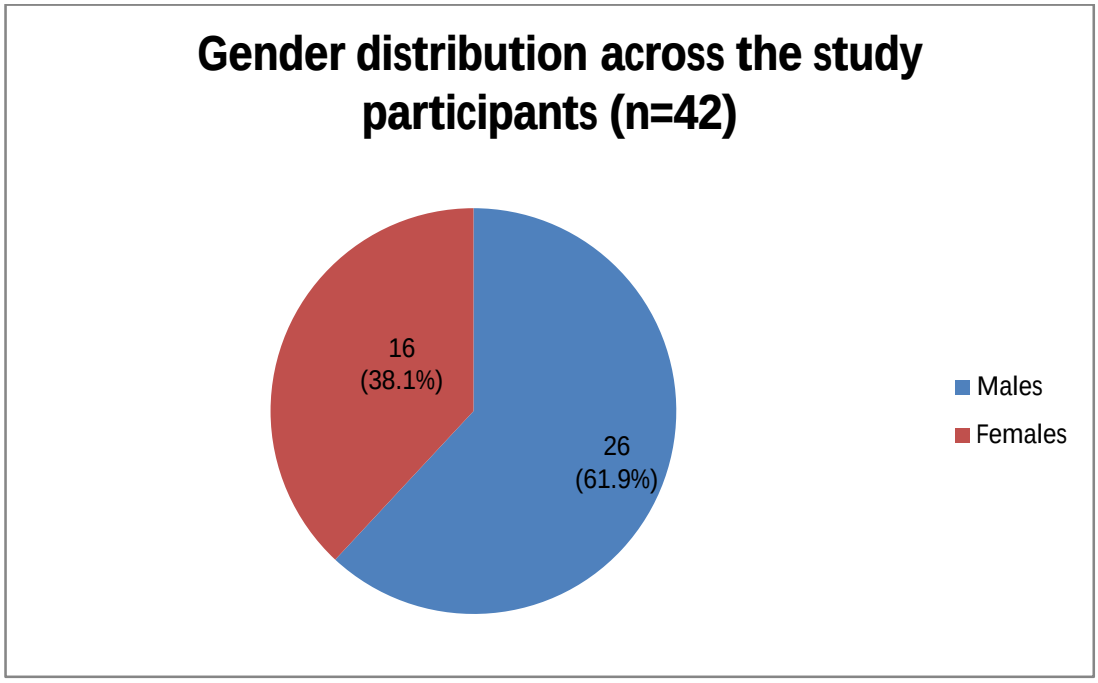


SEX DISTRIBUTION OF PATIENTS IN THIS STUDY

Among the 42 participants, 16 (38.1 %) were found to be females. 26 (61.9 %) of the total 42 participants were found to be males.

Gender distribution in this study

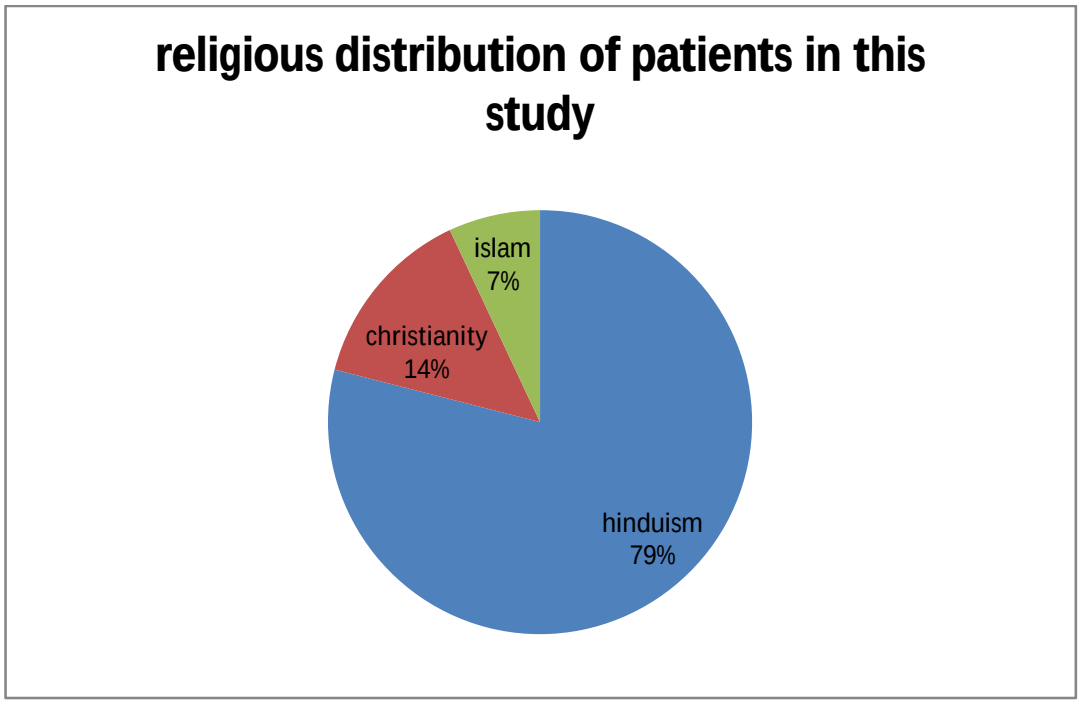
Gender	Frequency	Percentage
Male	26	61.9
Female	16	38.1
Total	42	100



Distribution of the patients in this study according to religion

6(14.2%) of the patients in my study were Christians ,3 (7 %) were Muslims and the rest 33(79%)were from Hinduism religion.

Religion	Frequency	Percentage
Hinduism	33	79
Islam	3	7
Christianity	6	14
Total	42	100



There is no statistically significant association of various religious cultures with incidence of nephrotic syndrome or its intravascular volume status.

For all the 42 patients, blood and urine samples were sent to test for

-serum electrolytes

-serum creatinine

-urine creatinine and

-urine electrolytes

The results were collected and FeNa was calculated for each patient using the given formula.

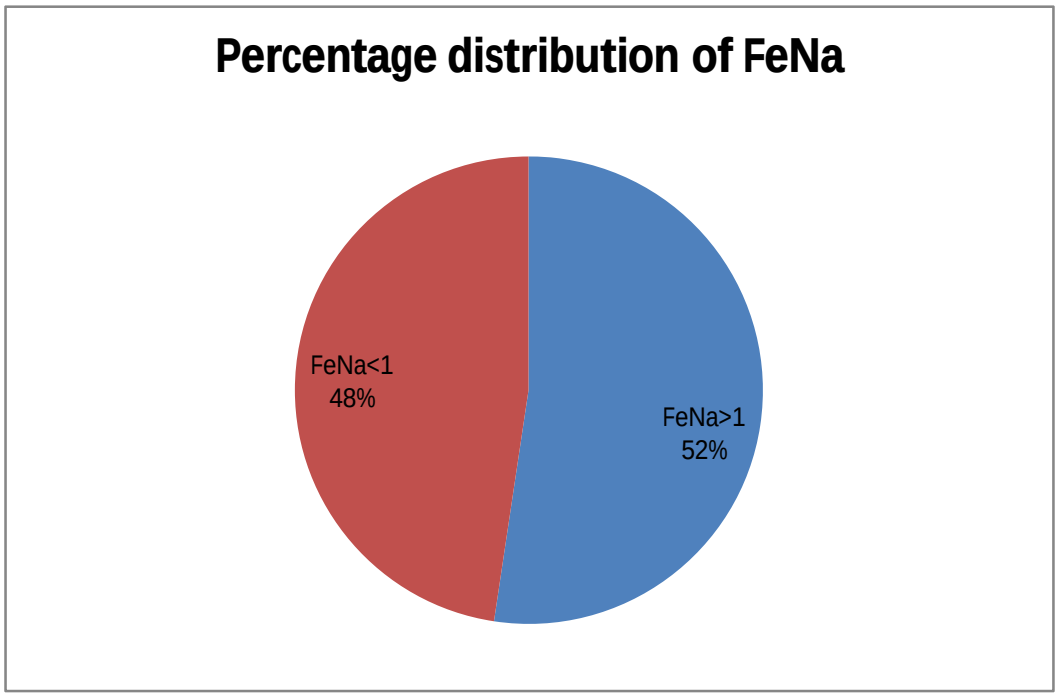
$$FeNa = \frac{UNa \times PCr \times 100}{PNa \times UCr}$$

A cutoff of FeNa as <1 or > 1 was taken.

20(47.6%) patients were found to have a FeNa of less than 1. 22(52.4%) out of the 42 patients were found to have a value of FeNa more than 1.

Percentage distribution of FeNa in this study

FeNa	Frequency	Percentage
<1	20	47.6
>1	22	52.4
Total	42	100



The first morning samples were also analyzed for urine electrolytes. From urine electrolytes, Fractional excretion of potassium was calculated from the below given formula-

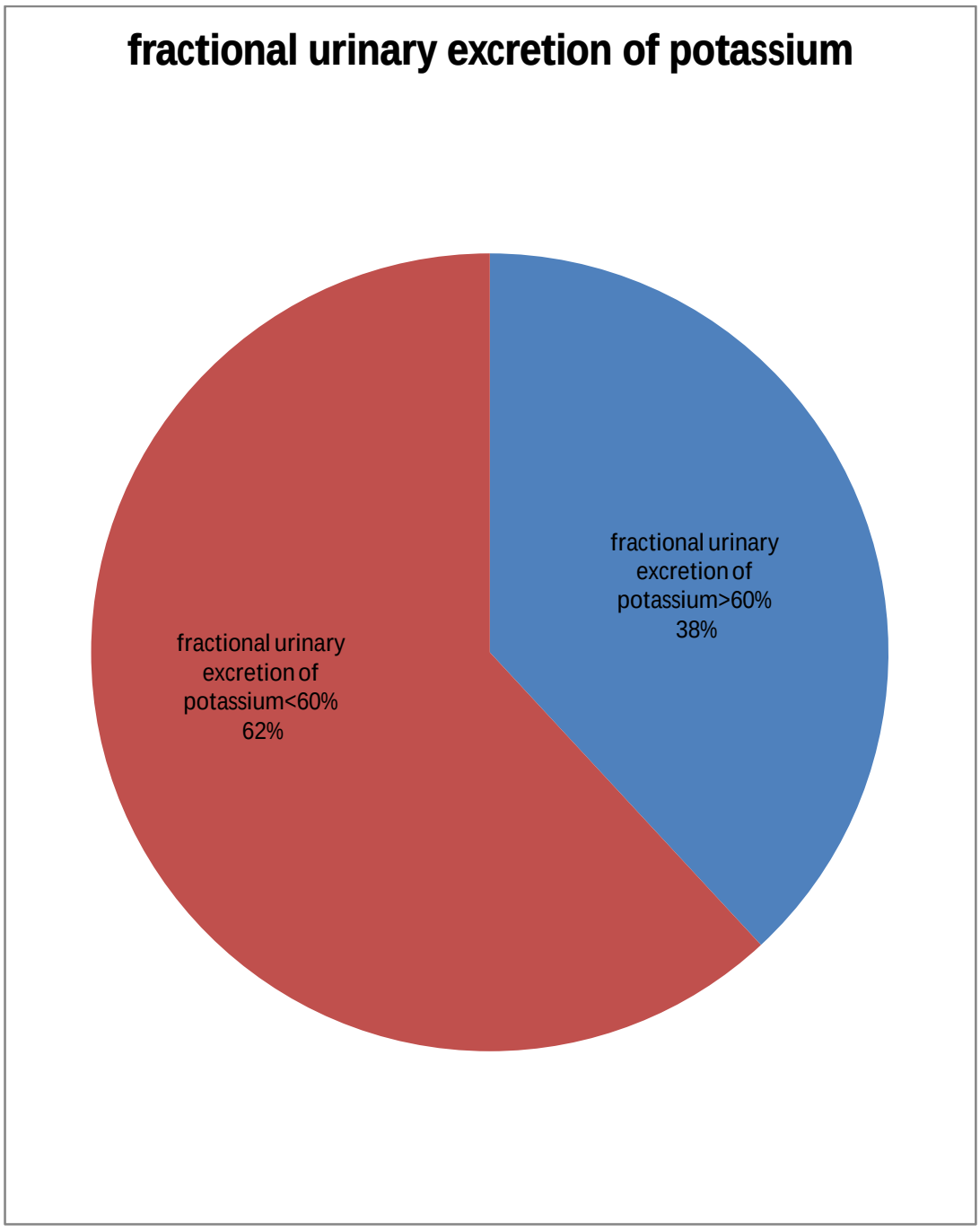
Fractional urinary potassium excretion- $\frac{Uk}{Uk+Una}$

A cutoff of 60 % of fractional urinary excretion of potassium was taken for classification.

16(38.1%) of the 42 patients were found to have a fractional urinary excretion of potassium of more than 60 % with a 95 % confidence intervals lying between 25 and 53 percentage points. 26 (61.9%) of the 42patients in this study had a fractional urinary excretion of potassium of less than 60 % with 95% confidence interval lying between 46 and 75 percentage points .

Distribution of fractional urinary excretion of potassium in this study

fractional urinary excretion of potassium	Frequency	Percentage
>60 %	16	38.1
<60 %	26	61.9
Total	42	100

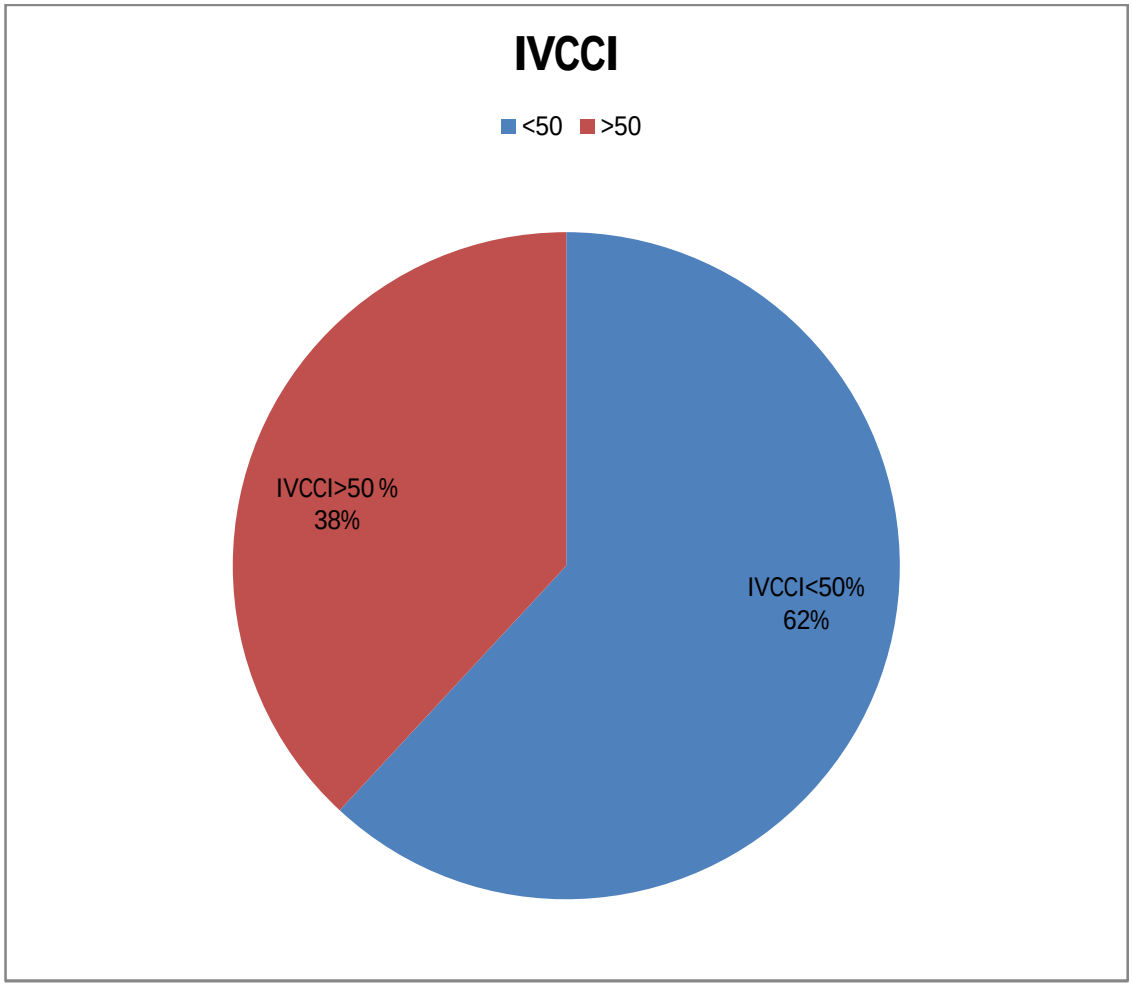


All the 42 patients in the study were taken for echocardiogram in the following day to Dept. of Pediatric Cardiology. IVC collapsibility was

measured in the subxiphoid views in both the long axis and short axis views. The results were averaged to arrive at a single value of IVCCI using the formula-

IVCCI-(IVC dia exp- IVC dia insp)/IVC dia exp

A cutoff of 50 % was taken. A total of 16(38.1%) out off 42 patients were found to a have an IVCCI < 50 % with a 95 % confidence intervals lying between 25 and 53 percentage points. 26(61.9 %) of the total patients were found to have an IVCCI > 50 % with 95% confidence interval lying between 46 and 75 percentage points .



Frequency of IVCCI in patients in this study

IVC collapsibility index	Frequency	Percentage
>50 %	16	38.1
<50 %	26	61.9
Total	42	100

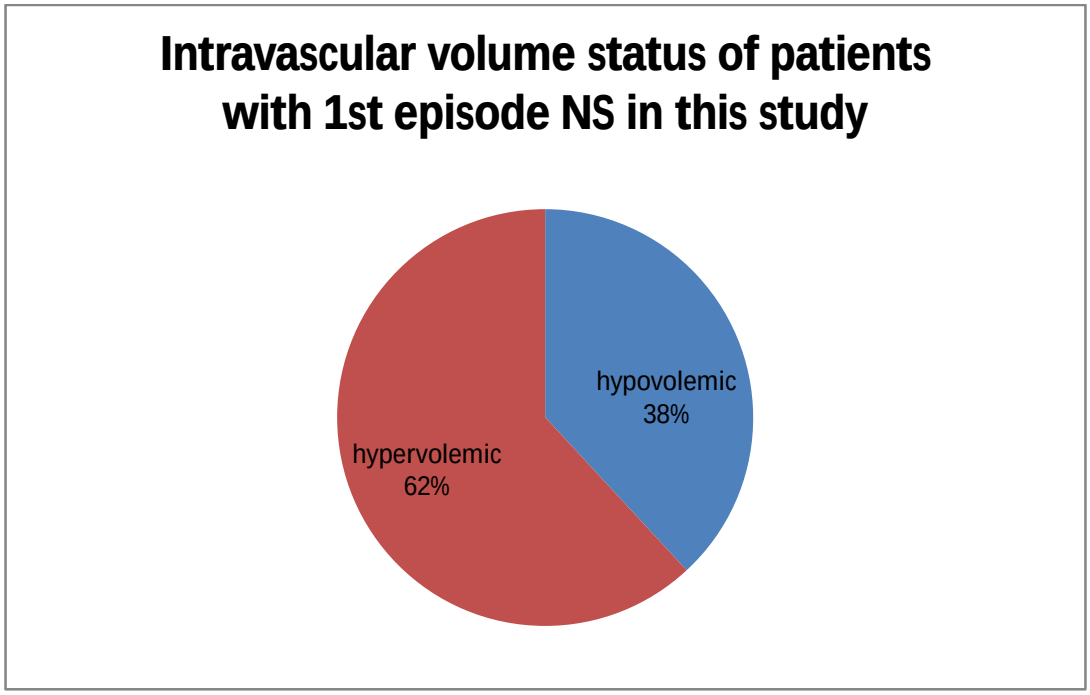
From the above values, hypovolemia was defined as having

- FENa<1 and
- Uk/Uk+Una>60% and
- IVC collapsibility > 50 %

In this study 16 (38.1%) patients had hypovolemia satisfying the above criteria% with a 95 % confidence interval lying between 25 – 53.2 percentage points. 22(52.4%) patients had FeNa >1 and fractional urinary potassium excretion <60 % and IVCCI < 50 % with a 95 % confidence interval lying between 37 – 67 percentage points. Hence these patients were classified as hypervolemic. 4(9.5%) patients had a FeNa <1 but fractional urinary potassium excretion <60 % and IVCCI < 50 %% with a 95 % confidence interval lying between 3 – 21 percentage points. Since these patients did not satisfy the criteria for hypovolemia fully, there were classified as having hypervolemic or normovolemic intravascular volume status. Hence a total of 16(38.1%) patients were classified as having hypovolemia whereas the rest of the 26(61.9 %) were classified as having hypervolemia or normovolemia(not having hypovolemia)with a 95% confidence interval lying between 37.4 to 67percentage points.

Volume status of the patients with 1st episode nephrotic syndrome in this study

Volume status	Frequency	Percentage	95 % confidence interval
hypovolemic (FeNa<1 and Urine pot >60% and IVC >50)	16	38.1	[25.0 – 53.2]
hypervolemic (FeNa<1 and Urinepot >60% and IVC >50) andnot satisfying criteria for hypovolemia	26	61.9	[37.4 – 67.1]
Total	42	100	


Intravascular volume status of patients with 1st episode NS in this study
hypovolemic 38%
hypervolemic 62%

DISCUSSION

The objective of this study was to measure the intravascular volume status of the patients presenting with first episode of nephrotic syndrome. Clinically intravascular status is very difficult to monitor because it is associated with many nonspecific signs and symptoms like giddiness, abdominal pain, diarrhea, hypertension etc. which can be very difficult to detect in children. Since diuretics are a major class of drugs used to treat edema in nephrotic syndrome, it was very vital to measure the intravascular volume status in patients for the treatment of edema.

In this study a total of 42 patients with first episode of nephrotic syndrome who were satisfying the inclusion criteria were included. Among the 42 patients , FeNa was found to be <1 in 20 patients denoting hypovolemia whereas it was >1 in 22 patients denoting hypervolemia. Fractional excretion of potassium was found to be >60 % in 16 patients making them hypovolemic whereas it was found to be less than 60 % in 26 patients making them hypervolemic. IVC CI was found out to be >50 % in 16 patients making them hypovolemic and in 26 patients it was less than 50 % making them hypervolemic.

A combination of FeNa < 1 ,fractional excretion >60% and IVCCI >50 % was taken as having a hypovolemic intravascular status. 16

patients in this study werefound satisfying the above criteria and were classified as having an HYPOVOLEMIC INTRAVASCULAR STATUS. The patients classified as having hypovolemic intravascular status didn't show any different symptoms or signs than the other subset of patients.

4 patients had a FeNa < 1 but fractional excretion of potassium <60 % and an IVCCI <50 %. Since these patients did not satisfy the criteria for hypovolemia they were classified as hypervolemia or normovolemia (not hypovolemia).

22 patients in this study had a FeNa > 1 and fractional excretion of potassium <60 % and an IVCCI <50 %. These patients were classified as having hypervolemic intravascular status.

Hence in this study it was found out that 16 patients out of 42 (38.1 %) had a HYPOVOLEMIC INTRAVASCULAR STATUS and 26 patients out of 42 (61.9%) had an INTRAVASCULAR STATUS WHICH WAS NOT HYPOVOLEMIC (HYPERVOLEMIC OR NORMOVOLEMIC). Since the patients with hypovolemia presented with almost the same symptoms as the ones with hypervolemia and diuretics are the drugs used to treat edema as first line, intravascular volume status must be assessed using laboratory parameters before the institution of diuretics to treat edema to prevent aggravation of a decreased intravascular volume status.

COMPARISON OF MY STUDY RESULTS WITH THE ONES DONE EARLIER

In a study published by Sahay et al in sep 2001 had concluded some patients with nephrotic syndrome are hypovolemic and urinary indices are very useful in the evaluation of intravascular volume status in nephrotic syndrome.

In a study published in March 2001 Osman domnez et al showed the usefulness of echocardiogram in measuring IVCCI,LAD in measuring the intravascular volume status in nephrotic syndrome.

In a recent study published n Turkish journal of medicine in Jan 2015 which was also done using FeNa, Fractional urine potassium and echocardiography, 25 % of the patients were found to be hypovolemic(FeNa <1,frac urine potassium excretion>60 % and ivcci>50,increased LAD) whereas the rest 75 % were found to be hypervolemic or normovolemic (FeNa >1,frac urine potassium excretion<60 % and ivcci<50,decreased LAD),the results of which are almost similar to my study.

LIMITATIONS IN MY STUDY

-There were some delays in transport of samples from 7 general pediatric wards to the biochemistry laboratory during busy admission days .

- In many patients the urine and sample were collected on the day of admission whereas echo was done in the following day due to restricted timings for echo.But it was made sure that diuretics were not used before performing the echo.

-the sample size of my study is only 42 in comparison to some previous studies which have done for a larger study group.

CONCLUSION AND RECOMMENDATIONS

The objective of this study was to determine the intravascular volume status in first episode of nephrotic syndrome. This was important because diuretics are the first line drugs used to treat edema in patients with nephrotic syndrome and if used in patients with hypovolemia , may precipitate further volume depletion which can lead to dangerous complications like renal vein, pulmonary vein, cerebral vessel thrombosis and acute tubular necrosis in the kidney. In this study it was noted that 38% patients were hypovolemic which is a significant percentage. Hypovolemia in nephrotic syndrome can be clinically silent but can be detected by simple tests like FeNa ,fractional urinary potassium and echocardiography to measure IVCCI which are commonly available in many centers and are relatively inexpensive.

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ABBREVATIONS

NS - Nephrotic syndrome

SRNS - Steroid Resistant Nephrotic Syndrome

SDNS-Steroid dependent nephrotic syndrome

MCD - Minimal Change Disease

FSGS - Focal Segmental Glomerular Sclerosis

MPGN - Membrano Proliferative Glomerulo Nephritis

DMP - Diffuse Mesangial Proliferation

MN - Membranous Nephropathy

GBM - Glomerular Basement Membrane

GFR - Glomerular Filtration Rate

LM - Light Microscopy

EM - Electron Microscopy

IF - Immuno Fluorescence

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.Krishnan.V.P.
PG in M.D.(Paediatrics)
Institute of Child Health
Madras Medical College
Chennai 600 003

Dear Dr.Krishnan.V.P.

The Institutional Ethics Committee has considered your request and approved your study titled **"INTRA-VASCULAR VOLUME STATUS IN FIRST EPISODE NEPHROTIC SYNDROME "** NO.59012015.

The following members of Ethics Committee were present in the meeting hold on 20.01.2015 conducted at Madras Medical College, Chennai 3.

1. Prof.C.Rajendran, MD	:Chairperson
2. Prof.R.Vimala,MD.,Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi,MD.,Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.R.Nandini,MD.Director, Inst.of Pharmacology,MMC	: Member
5. Prof.P.Ragumani, MS., Professor, Inst.of Surgery,MMC	: Member
6. Prof.K.Ramadevi, Director , Inst.of Bio-Chem.MMC	: Member
7. Prof.Saraswathy,MD.,Director,Pathology, MMC	: Member
8. Prof.Md.Ali, MD., DM.,Prof.&HOD of Medl.GE,MD.MMC	: Member
9. Thiru S.Rameshkumar, B.Com., MBA.,	: Lay Person
10.Thiru S.Govindasamy, BA., BL.,	: Lawyer
11.Tmt.Arnold Saulina, MA., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

Sys 2

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

INFORMED CONSENT FORM

Study place: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

Title of the study: **INTRAVASCULAR VOLUME STATUS IN 1ST EPISODE NEPHROTIC SYNDROME**

Name of the investigator : V.P.KRISHNAN

Name of the Participant: Age: Sex:

Hospital number: Blood sample no:

1. I have read and understood this consent form and the information provided to me regarding the participation in the study.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have informed the investigator of all the treatments I am taking or have taken in the past including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.*

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *

8. I have not participated in any research study in the past.

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *

11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information

given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு : நெப்ராப்டிக்ஸ் சிண்ரோமால் முதன்முறை பாதிக்கப்பட்ட குழந்தைகளின் இரத்தக் குழாய் இருப்பின் அளவு மாற்றம் குறித்து ஒரு ஆய்வு.

இடம் : அரசு தாய்சேய் நல மருத்துவமனை, எழும்பூர், சென்னை-8.

குழந்தையின் பெயர் : தேதி :

த/பெயர் : உள்/வெளி நோயாளி எண் :

வயது : ஆராய்ச்சி சேர்க்கை எண் :

..... என்பவராகிய நான் இந்த ஆய்வின் விவரங்களை படித்து தெரிந்து கொண்டேன் (அல்லது) எனக்கு படித்து காண்பிக்கப்பட்டது. அதன் நோக்கங்களும் முறையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்குகொள்ள சம்மதிக்கிறேன்.

1. இந்த ஒப்புதல் படிவத்தை நான் படித்து புரிந்து கொண்டேன்.
2. இச் சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.
3. இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது.
4. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றி அறிந்து கொண்டேன்.
5. இந்த ஆய்வில் என் குழந்தைக்கு ஏற்படும் நோயின் தன்மையும் மற்றும் வளர்ச்சியை ஆறு மாதம் வரை கண்காணிப்பதின் முக்கியத்துவம் எனக்கு விளக்கப்பட்டது.
6. இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.
7. ஆய்வாளர் இந்த ஆய்வில் என் குழந்தையின் பங்களிப்பை எந்த நேரத்திலும் எந்த காரணத்திற்காகவும், எவ்வித ஒப்புதல் இல்லாமலும் நிறுத்திக் கொள்ளலாம் எனவும் தெரிந்து கொண்டேன்.
8. இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என் குழந்தையிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸடிட்யூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.
9. இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது என் குழந்தையின் பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.
10. எனது எல்லா கேள்விகளுக்கும் திருப்திகராமாக பதிலளிக்கப்பட்டது.
11. இந்த ஆராய்ச்சியில் பங்களிக்க வேண்டுமென முடிவு செய்துள்ளேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

எனது குழந்தைக்கு ஏற்படும் நோயின் தன்மையையும் மற்றும் வளர்ச்சியை 6 மாதம் வரை கண்காணிப்பதற்கு அனுமதி தருகிறேன்.

இச்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

பங்கேற்பாளர்

பங்கேற்பாளருடைய பெயர் மற்றும் கையொப்பம்/கைரேகை (அல்லது சட்ட ரீதியான பிரதிநிதி - சட்டரீதியான பிரதிநிதி - பங்கேற்பாளர் செயல்திறமையற்றவராக இருந்தால் / 17 வயதிற்கு கீழ்உள்ளவர்களுக்கு - பெற்றோர் / பாதுகாவலர்)

....

பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் பெயர் மற்றும் கையொப்பம் (படிப்பறிவு இல்லாத மக்களுக்கு)

....

பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் முகவரி மற்றும் தொலைபேசி எண்

....

ஆராய்ச்சியாளரின் பெயர் கையொப்பம் தேதி

INFORMATION SHEET

Place of study: INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN

Name of Investigator : V.P.KRISHNAN

Name of Participant Age: Sex:

Hospital No:

Study title: **INTRAVASCULAR VOLUME STATUS IN 1ST EPISODE NEPHROTIC SYNDROME**

• We are conducting a study of assessing intravascular volume status in 1st episode nephrotic syndrome. We request you to participate in the study

• The purpose of this study is to determine the intravascular volume status in children with nephrotic syndrome 1st episode and determine the safety of use of diuretics to decrease edema. .

•This will be done by testing FeNa and fractional potassium excretion in urine and assessment of IVC collapsibility index by Echocardiogram.

• The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

• Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

• The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator

Signature of

Parent/Gaurdian

Date:

Name and signature / thumb impression of the participant /parents/guardian

Name _____ Signature_____
Date_____

Name and Signature of impartial witness:

Name _____ Signature_____
Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____
Date_____

தகவல் படிவம்

ஆய்வு தலைப்பு : நெப்ராப்டிக்ஸ் சிண்ரோமால் முதன்முறை பாதிக்கப்பட்ட குழந்தைகளின் இரத்தக் குழாய் இருப்பின் அளவு மாற்றம் குறித்து ஒரு ஆய்வு.

இடம் : அரசு குழந்தை நல மருத்துவமனை, எழும்பூர், சென்னை-8.

குழந்தையின் பெயர் : தேதி :

த/பெயர் : உள்/வெளி நோயாளி எண் :

வயது : ஆராய்ச்சி சேர்க்கை எண் :

பாலினம் :

தங்கள் குழந்தையும் இந்த ஆய்வில் பங்கு பெற கேட்டுக் கொள்கிறோம்.

1. நெப்ராப்டிக்ஸ் சிண்ரோமால் முதன்முறை பாதிக்கப்பட்ட குழந்தைகளின் இரத்தக் குழாய் இருப்பின் அளவு மாற்றம் குறித்து ஆராயப்படும். இதில் குழந்தைகளின் சிறுநீரில் பீனா பிராக்ஷனல் பொட்டாசியம் எஸ்கிரிஷியன். எக்கோ கார்டியோகிராமில் IVCCI பரிசோதனை செய்யப்படும்.
2. இது போன்ற ஆய்வு தென் இந்தியக் குழந்தைகளை வைத்து மிக குறைவான ஆய்வுகளே நடந்துள்ளன.
3. இதனால் குழந்தையின் நோய்வளர்ச்சி மற்றும் சிகிச்சைப் பலன்கள் பற்றி அறிந்து கொள்ள முடியும்.
4. இந்த ஆய்வில் கலந்து கொள்வதன் மூலம் என் குழந்தையிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸடிட்யூசனல் எத்திக்ஸ் கமிட்டினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.
5. உங்கள் குழந்தையை பற்றிய விபரங்கள் யாருக்கும் தெரிவிக்காமல் பாதுகாக்கப்படும்.
6. இந்த ஆய்வில் பங்கு பெறுவது உங்கள் தனிப்பட்ட விருப்பம் ஆகும். நீங்கள் இந்த ஆய்விலிருந்து எப்பொழுது வேண்டுமானாலும் விலகிக் கொள்ளலாம். அவ்வாறு விலகுவதால் குழந்தையின் சிகிச்சையில் எவ்வித பாதிப்பும் ஏற்படாது.
7. ஆய்வாளர் இந்த ஆய்வில் என் குழந்தையின் பங்களிப்பை எந்த நேரத்திலும் எந்த காரணத்திற்காகவும், எவ்வித ஒப்புதல் இல்லாமலும் நிறுத்திக் கொள்ளலாம் எனவும் தெரிந்து கொண்டேன்.

8. ஆய்வில் பங்குகொள்ளும்போது ஏதேனும் சந்தேகம் ஏற்பட்டால் ஆய்வாளரை தொடர்பு கொள்ளலாம்.

இச்சுய தகவல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்று தெரிவிக்கிறேன். இச்சுய படிவத்தின் ஒரு நகல் எனக்கு கொடுக்கப்படும் என்று தெரிந்து கொண்டேன்.

பங்கேற்பாளர்

பங்கேற்பாளருடைய பெயர் மற்றும் கையொப்பம்/கைரேகை (அல்லது சட்ட ரீதியான பிரதிநிதி - பங்கேற்பாளர் செயல்திறமையற்றவராக இருந்தால் / 17 வயதிற்கு கீழ் உள்ளவர்களுக்கு - பெற்றோர் / பாதுகாவலர்)

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பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் முகவரி மற்றும் கையொப்பம் (படிப்பறிவு இல்லாத மக்களுக்கு)

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பெயர் கையொப்பம்/கைரேகை தேதி

நடுநிலைமையிலுள்ள சாட்சியாளரின் முகவரி மற்றும் தொலைபேசி எண்

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ஆராய்ச்சியாளரின் பெயர் கையொப்பம் தேதி

DATA COLLECTION FORM

1. Name:
2. Age:
3. Gender:
4. Parent's name:
5. Address:

6. Phone number:
7. History :

8. Examination:

9.Lab parameters:

- FENa
- Uk/Uk+Una
- Serum osmolarity
- IVC collapsibility Index

S.No	Name	Age		gender		Lab parameters		
						FENa	UK/UK+Una(%)	IVC Collapsability Index(%)
1	prajitha	4		f		0.77	66	60
2	praveen	3.5		m		2.1	54	42
3	prem	5		m		1.7	56	40
4	hamsa	6		f		3.1	40	43
5	gopi	4.5		m		2.2	38	45
6	monish	2		m		0.71	68	59
7	hansika	3		f		1.9	47	40
8	keerthi	2.5		f		4.1	30	34
9	karthi	5		m		0.69	72	78
10	sai dasin	6		m		3.45	42	22
11	akash	5		m		0.53	70	69
12	lavanya	5		f		2.6	52	43
13	tirumalai	4.5		m		0.6	75	70
14	rakesh	7		m		0.65	64	68
15	jansi	6		f		1.6	57	40
16	rani	1.5		f		0.8	65	71
17	deepika	7.5		f		2.46	48	32
18	kailash	8		m		2.7	40	34
19	sai laxmi	2		f		0.7	72	62
20	arasi	2		f		0.5	77	80
21	ragavi	3		f		3.8	40	38
22	raj	4		m		0.7	62	55
23	ahmed	8		m		1.7	40	40
24	george	4		m		0.66	45	48

25	eben	1.5		m		1.84	36	40
26	mohamad	2		m		2	50	42
27	swetha	4		f		0.81	56	48
28	rajesh	5		m		1.8	52	45
29	krishna	5		m		0.64	62	58
30	karim	4		m		2.2	55	44
31	ram	4		m		0.9	62	58
32	maya	3		f		1.9	40	40
33	james	2		m		0.84	47	45
34	lalit	6		m		0.34	82	78
35	jose	3		m		1.3	37	40
36	keerthana	6		f		0.8	40	45
37	madhu	6		f		0.59	79	65
38	joseph	5		m		2.8	41	34
39	priya	5		f		0.25	88	81
40	arun	4		m		1.9	44	42
41	amarnath	8		m		0.24	80	73
42	thomas	7		m		1.3	52	46